THE VERSATILITY AND UTILIZATION OF PHOSPHORUS BASED COMPOUNDS IN CLASSIC CARBON-CARBON BOND FORMING AND ESTERIFICATION REACTIONS.

TETRADECYLTRIHEXYLPHOSPHONIUM CHLORIDE:
A recyclable phosphonium salt ionic liquid for Suzuki cross-coupling reactions of aryl halides under mild conditions.

DIMETHYLMALONYLTRIALKYLPHOSPHORANES:
New general reagents for esterification reactions allowing controlled inversion or retention of configuration on chiral alcohols.

By: Jeffrey C. H. Dyck, B.Sc.

A Thesis submitted to the Department of Chemistry in partial fulfillment of the requirements for the degree of Master of Science.

September 2003
Brock University
St. Catharines, Ontario

TABLE OF CONTENTS

FIGURES

SCHEMES

TABLES

ABBREVIATIONS

BPO	benzoyl peroxide
$CDCl_3$	deuterated chloroform
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMF	dimethylformamide
DMM	dimethyl malonate
DMSO	dimethyl sulfoxide
DMTP	dimethylmalonyltributylphosphorane
Et_3N	triethylamine
EtOAc	ethyl acetate
FTIR	Fourier Transform Infrared
GC	Gas Chromatography
HPLC	High Pressure Liquid Chromatography
HREIMS	High Resolution Electron Ionization Mass Spectroscopy
KBr	potassium bromide
K_3PO_4	potassium phosphate
MS	Mass Spectroscopy
Na_2CO_3	sodium carbonate
Na_2SO_4	sodium sulphate
NMR	Nuclear Magnetic Resonance
$Pd_2(dba)_3$	palladium dibenzilidene acetone
PhMe	toluene
THF	tetrahydrofuran
THPC	tetradecyltrihexylphosphonium chloride

ACKNOWLEDGEMENTS

I would be remiss if I did not firstly thank Dr. James McNulty for the opportunity to pursue my education under his supervision. Along the way I have benefited greatly from your expansive knowledge, valuable direction and passion for research. I am also appreciative of the perspective and insights provided by Dr. Fred Capretta and Dr. Al Robertson as members of my thesis committee.

One might say that the only thing better than one Jeff is two. I offer special thanks to Jeff Wilson for the many years of symbiotic existence in the lab. Thanks also to Vladimir Laritchev for your assistance on various projects and intelligent advice.

Additionally, no research project would be completed without the dedicated work of Tim Jones, John Vandenhoff, Chris Skorski, Olga Bukovec, and Veronica Grunner.

A debt of gratitude is also owed to my family and friends who have always been a great support and encouragement (even when nobody understood what I was talking about).

Finally, my deepest thanks is reserved for my wife, Amber Dyck, for shining a light in my eyes when the light at the end of the tunnel was difficult to see. For your unconditional love and support, encouragement, inspiration, motivation, assurance, and reassurance, I am forever grateful.

ABSTRACT

I. SUZUKI CROSS-COUPLING REACTION

The phosphonium salt room temperature ionic liquid tetradecyltrihexylphosphonium chloride (THPC) has been employed as an efficient reusable media for the palladium catalyzed Suzuki cross-coupling reaction of aryl halides, including aryl chlorides, under mild conditions. The cross-coupling reactions were found to proceed in THPC containing small amounts of water and toluene (single phase) using potassium phosphate and 1% $Pd_2(dba)_3 \cdot CHCl_3$. Variously substituted iodobenzenes, including electron rich derivatives, reacted efficiently in THPC with a variety of arylboronic acids and were all complete within 1 hour at 50^0C. The corresponding aryl bromides also reacted under these conditions with the addition of a catalytic amount of triphenylphosphine that allowed for complete conversion and high isolated yields. The reactions involving aryl chlorides were considerably slower, although the addition of triphenylphosphine and heating at 70^0C allowed high conversion of electron deficient derivatives. Addition of water and hexane to the reaction products results in a triphasic system, from which the catalyst was then recycled by removing the top (hexanes) and bottom (aqueous) layers and adding the reagents to the ionic liquid which was heated again at 50^0C; resulting in complete turnover of iodobenzene. Repetition of this procedure gave the biphenyl product in 82-97% yield (repeated five times) for both the initial and recycled reaction sequences.

II. Esterification Reaction

A new class of trialkylphosphorane has been prepared through reaction of a trialkylphosphine with 2-chlorodimethylmalonate in the presence of triethylamine. These new reagents promote the condensation reaction of carboxylic acids with alcohols to provide esters along with trialkylphosphine oxide and dimethylmalonate. The condensation reaction of chiral secondary alcohols can be controlled to give either high levels of inversion or retention through a subtle interplay involving basicity of the reaction media, solvent, and tuning the electronic and steric nature of the carboxylic acid and steric nature of the phosphorane employed. A coherent mechanism is postulated to explain these observations involving reaction via an initial acyloxyphosphonium ion.

INTRODUCTION

I. IONIC LIQUIDS

In the past several years the chemical industry has made great strides to improve both its public image and environmental impact. The Responsible CARE program is a direct result of these efforts. As part of the program, companies strive to promote public awareness within the community and take a proactive role in measuring and reducing any negative impact on the community and/or environment resulting from the activities of the company. With this in mind it is no wonder that there has been a major effort to develop new processes that incorporate cleaner technologies, not only throughout industry, but in academia as well. One such area focuses on reducing or eliminating the use of damaging solvents. Volatile solvents are one of the most damaging chemicals simply due to the large quantities used in synthesis.[1] As a result, containment and disposal issues arise that cannot always be treated in an environmentally friendly manner. The introduction of ionic liquids as solvents has the potential to alleviate these problems in a number of ways, and are thus commonly referred to as "green solvents".

Firstly, the definition of an ionic liquid is rather self-explanatory, simply put; they are liquids that consist solely of ions. Furthermore, these compounds have melting points below 100^0C. Those compounds that satisfy the former criteria but exhibit melting points greater than 100^0C are known as molten salts. Typically these compounds are highly corrosive and highly viscous, compared to the relatively low viscosity of ionic liquids.[2]

Besides the properties that satisfy the aforementioned definition, one of the most attractive is that ionic liquids have no measurable vapour pressure. Ionic liquids also exhibit several other characteristic properties such as, thermal stability, density, solvation strength and solubility, and acidity. Besides vapour pressure, any or all of the properties of a given ionic liquid can be altered by careful manipulation of the cation, anion, or both. The most commonly used ions in the composition of ionic liquids are shown in Figures 1&2.

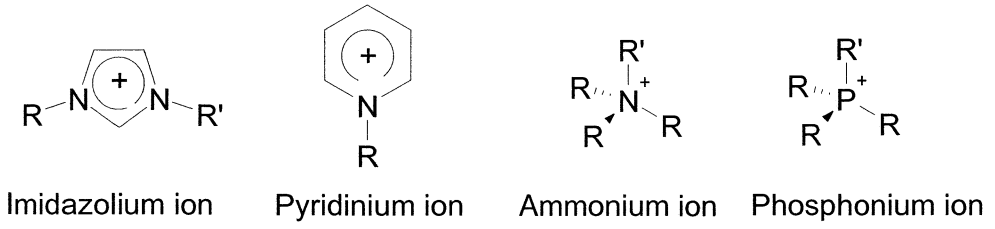


Figure 1. Common Cations in Ionic Liquids

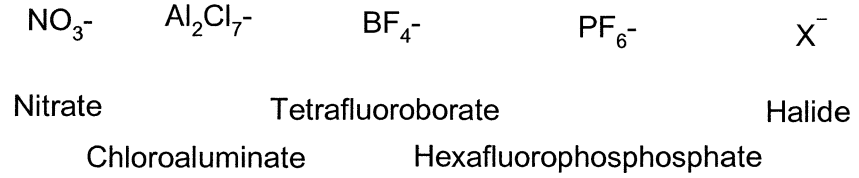


Figure 2. Common Anions in Ionic Liquids

Each property is governed by a unique set of trends that have been extensively studied and described by Wasserscheid.[3] It is because of this great diversity and variability that ionic liquids have also gained the reputation as "designer solvents".

Several methods exist for the synthesis of ionic liquids as well as for the manipulation of cations and anions. It should be noted that the focus of this paper is not

on the synthesis of ionic liquids, rather their application as "green solvents" in classic organic reactions. Therefore, the reader is referred to previous reviews on the topic[1,3] for a description of procedures for the production of ionic liquids.

There are several factors that make ionic liquids a particularly good alternative to conventional solvents. They are good solvents for a wide range of inorganic and organic materials such that unusual combinations of reagents can be brought together in the same phase. As mentioned earlier ionic liquids can be altered to fit a specific purpose, such as solvent polarity. By manipulating the ions, several different ionic liquids can be made which have polarities similar to a wide range of solvents including DMF, DMSO, methanol and water. The acidity of the ionic liquid can also be varied in much the same way, as seen in Figure 3.[3]

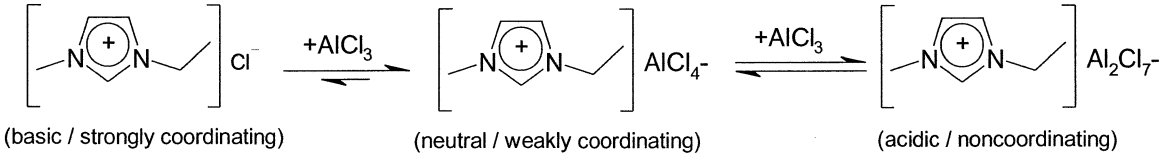


Figure 3. Control of the Acidity of Ionic Liquids

The fact that ionic liquids have no measurable vapour pressure allows for easy distillation of products from the reaction mixture when using ionic liquids as opposed to volatile solvents. In the case of ionic liquids, the problem of azeotrope formation is avoided, as is the removal of trace amounts of organic compounds, which is often difficult to achieve.[4] Finally, and perhaps most significantly is that ionic liquids have the ability to form biphasic systems due to their immiscibility in a number of organic solvents and/or water.

This is particularly important for reactions where a transition metal catalyst is required to mediate the process. These are most often homogenous catalysts that are sometimes difficult to separate from the reaction products in typical organic solvents. As a result, there is the real possibility and likelihood that there may be some toxic catalyst contamination of final products. However, in a biphasic system made up of ionic liquid and some other solvent, the transition-metal catalyst remains in the ionic phase while the products and reagents are soluble in the organic phase. Ionic liquids are therefore called immobilizing agents for biphasic catalysis. With vigorous stirring the two phases interact sufficiently for the reaction to take place, as shown in Figure 4.

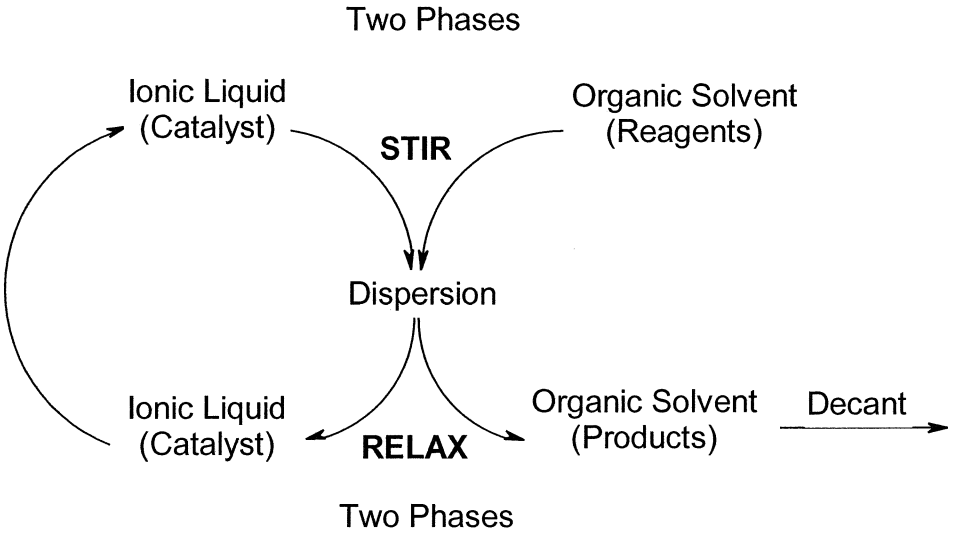


Figure 4. Biphasic Reaction System

When stirring is stopped, the phases separate which allows for simple decantation of the products. Furthermore, the ionic liquid may be reused many times without the addition of further catalyst, thus, increasing its efficiency while drastically reducing solvent and inorganic wastes.[1] In some cases a mixture of organic solvent, ionic liquid and water form a triphasic system in which products are retained in the organic phase, salt by-

products in the aqueous phase, and transition metal catalyst in the ionic liquid phase. This system also allows for ease of product separation and catalyst reuse.

It is important to consider that in a biphasic system, consisting of water as one of the phases, the ionic liquid must be water stable. Unfortunately, chloroaluminate melts are highly hygroscopic and labile towards hydrolysis.[3] Additionally, many organic substrates and organometallic compounds are not chemically inert in these particular ionic liquids, therefore, their use in biphasic systems is severely limited.[4] Nevertheless, a large number of ionic liquids exist which are stable to ambient temperature, air and water. These have great potential as immobilizing agents in biphasic catalysis for a large number of organic reactions. It has also been shown that ionic liquids can act as the sole solvent for many organic reactions, including but not limited to transition-metal catalyzed processes. Once the reaction is complete, a biphasic or triphasic system is created upon the addition of solvents and/or water as part of the workup procedure.

The use of ionic liquids as solvents can be separated into two major types of reactions; those that do not require an organometallic catalyst and those that do. Beginning with the former, some of the most common and successful reactions performed in ionic liquids are the Diels-Alder reaction[5], Friedel-Crafts reaction[6], Fischer Indole synthesis[7], and the Beckmann rearrangement[8], to name only a few. Reaction rates can be significantly increased by using ionic liquids as solvents, and in some cases regioselectivity is also enhanced. Ionic liquids have gained great popularity in reactions mediated by organometallic catalysts, due in part to their ability to immobilize transition-metal catalysts. One such reaction that has benefited considerably from the advent of ionic liquids is hydrogenation. Reaction rates are up to five times faster in ionic liquids

than conventional solvents[9], while chemoselectivity is also increased when more than one site exists for hydrogenation. Moreover, ionic liquids have been found to mediate, and improve, stereoselective reactions in which a chiral catalyst is used. This opens up an entire new dimension of applications for ionic liquids, as asymmetric synthesis is one of the most important and fastest growing areas of organic chemistry. These findings have spawned the rush to incorporate chiral cations and/or anions in the synthesis of new chiral ionic liquids. Most often chiral molecules are taken from Nature's "chiral pool" and manipulated to produce chiral ions that are used in the synthesis of ionic liquids.[10] Several chiral ionic liquids can be seen in Figure 5.[11]

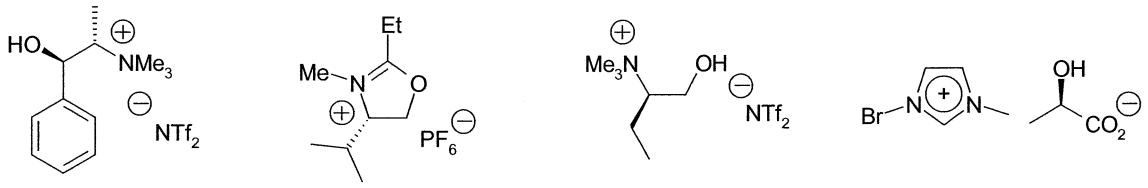


Figure 5. Examples of Chiral Ionic Liquids

Already several of these chiral ionic liquids have found applications in organic chemistry either as co-catalysts or as chiral solvents that contribute to stereoselective induction.

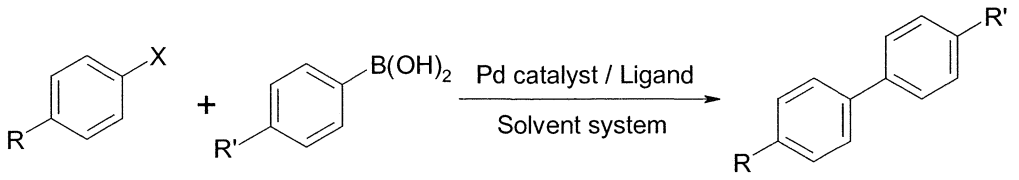
Besides hydrogenation, a large number of reactions exist in which ionic liquids have been used with favourable results. These include hydroformylations[12], oxidations[13], oligomerizations and polymerizations[14,15,16], C-C cross-couplings, and many more. A comprehensive study of the applications of ionic liquids in these and many more organic syntheses has already been reviewed and is available elsewhere.[2] Of special interest is the utilization of ionic liquids in homogenous palladium-catalyzed C-C cross coupling reactions. These reactions comprise such "named" reactions as the Heck, Suzuki,

Sonogashira, Negishi, and Ullmann couplings, and have gained much attention as a result of their synthetic versatility.[4]

Biphasic systems have been applied to the palladium mediated Heck coupling reaction in quaternary nitrogen ionic liquids[17] and can be conducted at room temperature with the application of ultrasound.[18] The Suzuki reaction has also been carried out successfully in imidazolium ionic liquids both thermally[19] and with sonication.[20] Quaternary phosphonium salts on the other hand, are another class of readily available ionic liquid that have received scant attention in the literature. In one case, hexadecyltributylphosphonium bromide was used to affect Heck coupling of aryl halides with acrylic esters,[21] although the reaction was not efficient with aryl chlorides. It is thought that the use of quaternary phosphonium salts would find advantageous applications as the solvent in Suzuki reactions as well.

II. Suzuki Cross-Coupling Reaction

The Suzuki[22] cross-coupling reaction has become a standard method for carbon–carbon bond formation between an sp^2 or non-β-hydride containing electrophile and a boronic acid derivative (Scheme 1).



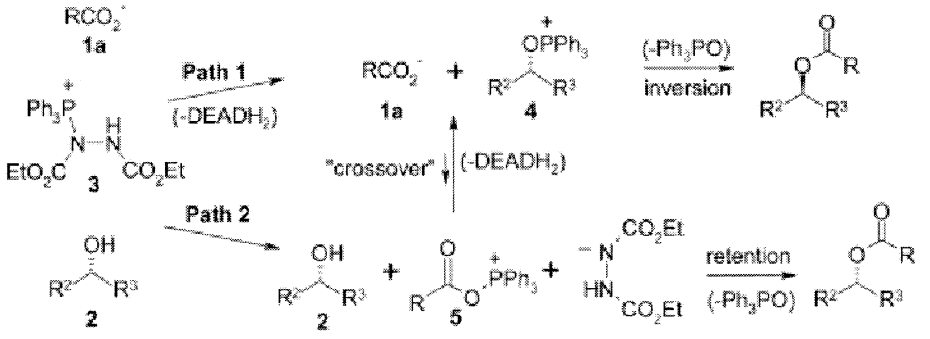
Scheme 1. Suzuki Cross-Coupling Reaction

Recent application of the reaction to aliphatic electrophiles[23] has expanded its scope considerably. Much recent effort has gone into devising new ligands for this palladium mediated process and various electron rich alkyl phosphines[24,25] and mixed aryl/alkyl phosphine ligands[26,27] have been described. Systems allowing for couplings of aryl chlorides are especially sought after due, in part, to the lower cost and ready availability of these substrates and a number of catalysts have recently been developed which promote their Suzuki coupling with boronic acid nucleophiles.[28,29] The number of applications for the Suzuki reaction increases appreciably as it becomes amenable to a greater number of reaction conditions and systems. Currently, one of the most promising uses is in the biaryl formation in the synthesis of natural products and novel pharmaceuticals.[22] It is reported herein on the use of the room temperature ionic liquid tetradecyltrihexylphosphonium chloride (THPC) as an efficient reusable media for the palladium catalyzed Suzuki cross-coupling reaction.

III. ESTERIFICATION REACTION

In a different vein, the Mitsunobu reaction[30,31,32,33] is a well-known and valuable reaction in organic synthesis, including, but not limited to, the synthesis of natural products and novel pharmaceuticals. It is widely employed in both condensation and displacement reactions of alcohols with various nucleophiles, normally proceeding with inversion of stereochemistry when chiral alcohols are utilized. The original process (Scheme 2) employed carboxylic acids **1** (or carboxylates **1a**) as the nucleophile producing ester or lactone products[31a] but has since been extended considerably to include a variety of both heteroatom and carbon-based nucleophiles.[31,34] The most commonly employed promoters for this reaction are dialkyl azodicarboxylates, such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), used in conjunction with triphenylphosphine. While these may be the classical promoters of the reaction, there has been a substantial amount of controversy in regards to the safety of DEAD. The current industrial processes for synthesizing DEAD are potentially explosive. DEAD is also shock-sensitive, light sensitive, unstable and toxic. Furthermore, shipping of this dangerous reagent is governed by several special regulations and requires exceptional care in handling. New reagents, such as the (cyanomethyl)trialkylphosphoranes,[35,36] have been developed which also result in inversion of stereochemistry on esterification of chiral alcohols.[35a] These new phosphoranes have also be employed in carbon-carbon[34,36b] and amination[36a] reactions with alcohols. The initial step of the DIAD/triphenylphosphine mediated esterification reaction[32,33] is understood to involve nucleophilic addition of triphenylphosphine to the

azodicarboxylate followed by proton transfer from a carboxylic acid to give **3** (Scheme 2).



Scheme 2. Mechanisms for the Mitsunobu Esterification Reaction

The subsequent steps involve nucleophilic attack of the alcohol **2** on **3** to form an activated alkoxyphosphonium salt **4**[31a] (Scheme 2, Path 1). Finally, S_N2-type displacement by the carboxylate anion on **4** with loss of triphenylphosphine oxide produces the ester with inversion of stereochemistry. Evidence for the existence of an alternative pathway for this reaction proceeding via an acyloxyphosphonium salt (such as **5**, Scheme 2) has been described by Jenkins[37] and Kunz.[38] More recently, DeShong[32b,39] demonstrated clear evidence for the involvement of an acyloxyphosphonium salt when hindered alcohols are involved and a further example of a Mitsunobu macrolactonization likely proceeding via the acyloxyphosphonium ion has also recently been described by Smith.[40] In these cases, lactone products were obtained exclusively with retention of stereochemistry. The competitive pathway leading to retention of stereochemistry with hindered alcohols via the acyloxyphosphonium ion **5** is outlined in Scheme 2, Path 2. This scheme also illustrates a competing view of the Mitsunobu reaction involving initial reaction along Path 2. The formation of the basic hydrazide anion leads to subsequent

alkoxide formation and "crossover" to the alkoxyphosphonium salt **4**,[32b,41] perhaps proceeding via a mixed alkoxy/acyloxy phosphorane-type intermediate,[33g,37a,42] ultimately yielding the ester with inversion of configuration as the normal outcome. The formation of a basic anion capable of alkoxide formation during the Mitsunobu processes described makes it difficult to differentiate between the direct reaction along Path 1 or initial reaction along Path 2 followed by the crossover leading to the necessary alkoxyphosphonium salt **4**. We have developed a new class of trialkylphosphorane reagent designed to allow for esterification under mild conditions that also helps delineate the competitive pathways described above.

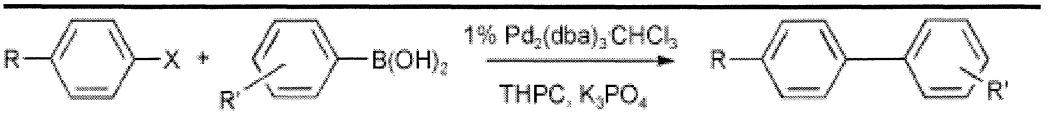
RESULTS & DISCUSSION

I. SUZUKI CROSS-COUPLING REACTION

The Suzuki cross-coupling reactions were found to proceed in THPC using various bases (Et_3N, $^{i}Pr_2NEt$, etc) but most efficiently when potassium phosphate and water (added for salt solubility) were employed. In order to maintain complete solubility of both the boronic acid and aryl halide in the ionic liquid, a small amount of toluene was added also. All of the reactions reported in Table 1 were therefore performed in an identical media (THPC, aryl halide, aryl boronic acid, $Pd_2(dba)_3{\cdot}CHCl_3$ (1%), K_3PO_4, H_2O, toluene) with the addition of triphenylphosphine in certain cases as noted. In many instances, the product biaryl crystallizes from the reaction media as the cross-coupling proceeds.

As can be seen from Table 1 (entries 1–9), the cross-coupling reaction of variously substituted iodobenzenes including electron rich derivatives (Table 1, entry 7) with a variety of arylboronic acids proceeded efficiently in THPC and were all complete within 1 h at 50°C. The reaction was chemoselective in the case of the mixed halide 4-chloroiodobenzene (Table 1, entry 9). The corresponding aryl bromides (Table 1, entries 11–13) also reacted under these conditions but proved to be somewhat more sluggish. We found that the addition of a catalytic amount of triphenylphosphine allowed for complete conversion and high isolated yields even for the electron rich substrates such as 4-methoxybromobenzene (Table 1, entries 12 and 13). As expected, reactions involving

aryl chlorides were considerably slower, however addition of triphenylphosphine and heating at 70°C allowed high conversion of 4-chloroacetophenone (Table 1, entries 14 and 15). The electron rich 4-methoxychlorobenzene was still slow to react under these conditions (Table 1, entry 16).



Entry	X	R	R′	Ligand	Temp./ °C	Time/h	Isolated yield (%)
1	I	H	H	None	50	1	95
2	I	Ac	H	None	50	1	100
3	I	Ac	2-Me	None	50	1	97
4	I	Ac	2-Napthyl	None	50	1	97
5	I	Ac	2-OMe	None	50	1	100
6	I	Ac	4-OMe	None	50	1	99
7	I	OMe	4-OMe	None	50	1	86
8	I	Me	4-OMe	None	50	1	92
9	I	Cl	4-OMe	None	50	1	90
10	Br	Ac	H	PPh_3	50	1	99
11	Br	Ac	4-OMe	PPh_3	50	1	98
12	Br	OMe	H	PPh_3	50	3	99
13	Br	OMe	4-OMe	PPh_3	50	3	95
14	Cl	Ac	H	PPh_3	70	30	84
15	Cl	Ac	4-OMe	PPh_3	70	30	76
16	Cl	OMe	4-OMe	PPh_3	70	30	17

Table 1. Pd Mediated Suzuki Cross-Coupling of Aryl Halides and Boronic Acids in THPC.

Addition of water and hexane to the reaction products in the phosphonium salt ionic liquid results in the formation of a triphasic system that differs from that reported for the imidazolium salts.[17] In the case of imidazolium salts, the ionic liquid is more

dense than water and forms the bottom phase with an aqueous central phase and organic layer on top. In the case of THPC, the palladium catalyst remains fully dissolved in the central phosphonium salt layer while the product biaryls are extracted into the top hexane phase and inorganic salts (phosphates/borates) into the lower aqueous phase (Figure 6).

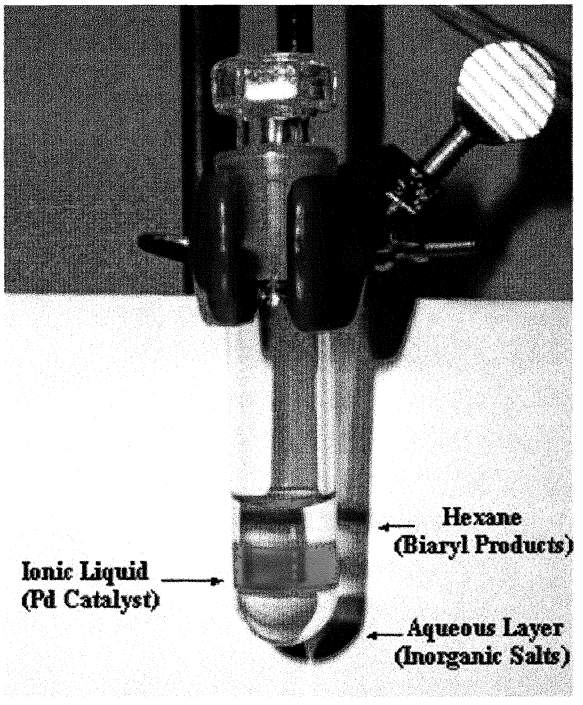


Figure 6. Triphasic System

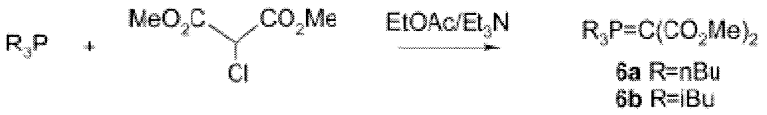
The reaction of phenylboronic acid with iodobenzene has been investigated extensively under our conditions in THPC. The yield obtained from hexane extraction and silica-gel chromatography of the hexane solubles ranged from 82–97% over several runs. On the other hand, direct filtration of the ionic liquid through a short silica-gel column gave slightly higher isolated yields, 95–97%. These results indicate that residual biaryls are still slightly soluble in THPC. The former procedure was more applicable towards the development of a catalyst recycling protocol since chromatography or filtration through silica would make re-use of the catalyst difficult. Thus, following

Method A (See Experimental Section), when further quantities of iodobenzene, phenylboronic acid and K_3PO_4, *but no further catalyst*, was added to the isolated central ionic liquid, heating again at 50°C resulted in complete turnover of iodobenzene. Repetition of the work-up Method A gave biphenyl in 82–97% yield (repeated five times) for both the initial and recycled reaction sequences. Thus it is clear that a competent palladium catalyst remains fully dissolved in the phosphonium salt allowing its efficient re-use.

The Suzuki cross-coupling reaction recently reported in imidazolium based ionic liquids requires ultrasonic irradiation to proceed at 30°C.[20] In addition, inactive Pd black is deposited during the reaction resulting in lower conversions (82–92%) with aryl iodides and bromides and particularly so in the case of electron deficient aryl chlorides (42–65%). Even when preformed Pd–biscarbene catalyst is used in this system, conversion of electron deficient aryl chlorides is low to moderate (39–66%).[20] The thermal Suzuki coupling reaction in these imidazolium based ionic liquids does not proceed with aryl chlorides, even at 110°C.[19] In contrast to these results, complete conversion of aryl iodides and bromides and high conversions with electron deficient chlorides can be achieved in the THPC ionic liquid without the use of a preformed catalyst at 50–70°C. The rapid coupling of aryl iodides and bromides and high conversions obtained with the aryl chlorides indicate that a very active catalyst is produced in the THPC system. In addition, the higher conversions and recyclability of this Pd THPC–catalyst system indicate the relatively high stability of the active Pd catalyst involved in the Suzuki coupling. Lastly, no homo-coupled products have been observed using the THPC catalyst system reported here.

II. ESTERIFICATION REACTION

A new class of trialkylphosphorane reagent, designed to allow for esterification under mild conditions and exemplified by dimethylmalonyltributylphosphorane **6a** (DMTP), was readily prepared by the reaction of a trialkylphosphine with α-chlorodimethylmalonate in the presence of Et_3N.



Scheme 3. Synthesis of Phosphoranes

The tributylphosphorane **6a** is a colourless, viscous oil stable under argon at room temperature for at least six months. When exposed to air, the oil slowly yields the products of its hydrolysis, tributylphosphine oxide and dimethylmalonate (DMM). Furthermore, DMTP undergoes significant colouration over time yielding a dark brownish/red solution. Many experiments were performed to optimize the reaction conditions and reduce or eliminate the colouration over time. The reaction was found to proceed smoothly in a variety of solvents (EtOAc, THF, DCM, Hexanes, etc.) with no effect on subsequent colouration. The effects of temperature, inert atmosphere, light, radical stabilizer, and solvent solution were also studied (Figure 7). Only temperature had any significant effect in reducing colouration. It was later discovered that an impurity in the chlorodimethylmalonate was responsible for the colouration. Using a

pure batch resulted in virtually no colour change, even at room temperature over one month.

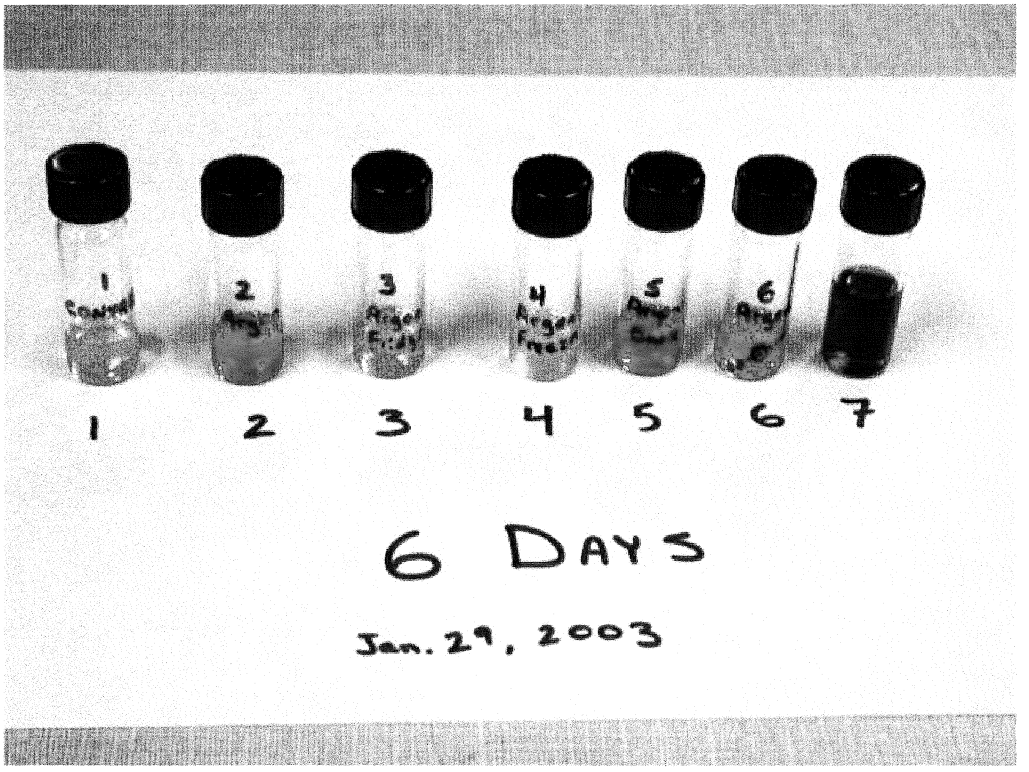
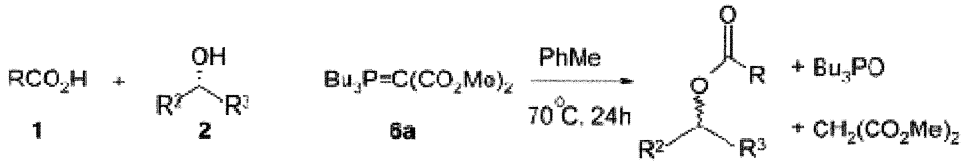


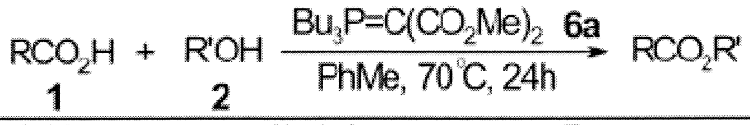
Figure 7. Colouration of DMTP Under Various Conditions

The DMTP reagent has been shown to effect the general condensation reaction of a wide variety of carboxylic acids **1** with simple alcohols **2** efficiently at neutral pH. The reactions were conducted in dry toluene under argon providing the ester product along with tributylphosphine oxide and DMM.



Scheme 4. General Esterification Reaction

Representative results are summarized in Table 2.



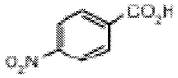
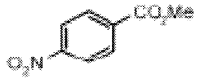
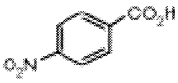
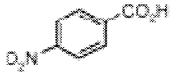
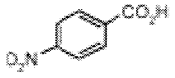
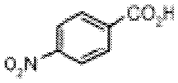
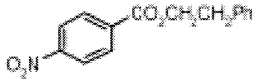
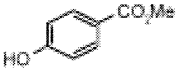
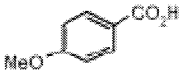
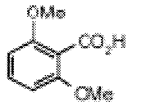
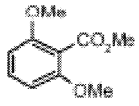
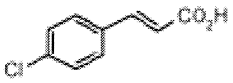
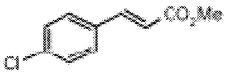
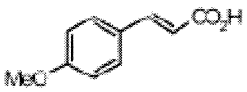
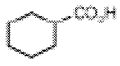
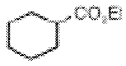
	Acid	Alcohol	Ester	Yield
1		CH_3OH		94%
2		CH_3CH_2OH		86%
3		$(CH_3)_2CHCH$		83%
4		$(CH_3)_3COH$		N.R.
5		$PhCH_2CH_2OH$		88%
6		CH_3OH		70%
7		CH_3OH		98%
8		CH_3OH		75%
9		CH_3OH		75%
10		CH_3OH		77%
11		CH_3OH		70%
12		CH_3OH		81%
13		CH_3CH_2OH		78%

Table 2. Esterification Reactions Promoted by DMTP.

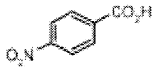
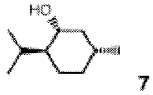
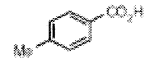
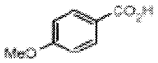
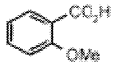
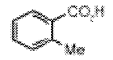
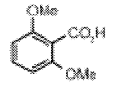
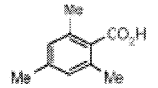
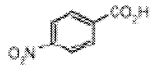
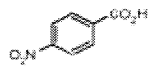
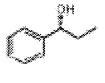
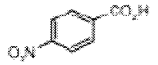
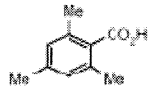
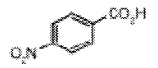
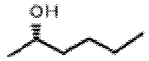
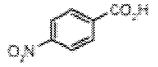
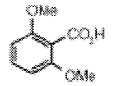
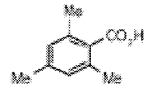
Yields are high with methanol and drop slightly as the bulk of the alcohol increases (Table 2, entries 1-3) while no reaction occurred with the tertiary alcohol *tert*-butanol (Table 2, entry 4). The β-aryl alcohol 2-phenyl-1-propanol reacted cleanly without styrene formation (Table 2, entry 5), indicating that β-elimination does not occur. Electron-deficient benzoic acids gave slightly better yields (Table 2, entries 1 and 7) with the same alcohol (compare to entries 6 and 8-10). The reaction may also be carried out successfully in the presence of a free phenol (Table 2, entry 8). Finally, cinnamic and aliphatic acids appear to react without difficulty (Table 2, entries 11-13).

A clear advantage gained when using DMTP is that the side products tributylphosphine oxide and DMM can be largely removed by aqueous base partition (0.2 M Na_2CO_3) thereby simplifying purification. The yields reported in Table 2 pertain to the isolated mass of the purified esters obtained by silica gel chromatography.

The stereochemical implications of the reaction were then investigated utilizing chiral alcohols L-menthol **7**, the secondary aliphatic (*2S*)-hexanol **8**, and the benzylic (1*R*)-1-phenyl-1-propanol **9** under a variety of conditions (Scheme 5).

Scheme 5. Esterification Reactions Investigating Stereochemistry.

The reaction could be carried out successfully in toluene, THF, 1,2-dichloroethane, ethyl acetate, or DMF, however, we determined that toluene and DMF gave slightly higher yields and often complementary results in terms of inversion and retention ratios. The overall results are summarized in Table 3.

	Acid	Alcohol	Solvent	Conv.[a]	Ret:Inv[b]
1		 **7**	PhMe	82	95:5
2		7	PhMe	53	63:37
3		7	PhMe	52	33:67
4		7	PhMe	28	2:98
5		7	PhMe	27	5:95
6		7	PhMe	56	4:96
7		7	PhMe	78	<0.5:>99.5
8		7	DMF	76	99.2:0.8
9		 **9**	DMF	61	64:36
10		**9**	DMF	27[c]	95:5
11		**9**	PhMe	83	5:95
12		 **8**	DMF	71	80:20
13		**8**	DMF	34[c]	97.0:3.0
14		**8**	PhMe	85	<0.1:>99.9
15		**8**	PhMe	84	<0.1:>99.9

[a] Conversions are unoptimized results based on the isolated mass of purified ester after the standard 24 h reaction period.
[b] Retention : inversion ratios measured by ^{1}HNMR (menthol) and chiral GC or HPLC in comparison with authentic standards
[c] Bulky phosphorane **6b** (isobutyl) used to promote esterification.

Table 3. Stereoselective esterification Reactions Promoted by DMTP.

The reaction of L-menthol **7** with 4-nitrobenzoic acid promoted by phosphorane **6a** in toluene provided the ester with 95% retention of configuration (Table 3, entry 1). The degree of inversion increased as the electron donating ability of the 4-substituent increased (Table 3, entries 1-3) while conversion was higher when electron-deficient 4-substituted benzoic acids were employed. We next investigated the steric nature of the acid with remarkable results. Even a single ortho substituent was seen to have a considerable effect on the outcome of the reaction now delivering the product of inversion with high selectivity (Table 3, entries 4-7). The conversions were lower when mono-ortho-substituted benzoic acids were employed due to competitive formation of the acid anhydride. The reaction of L-menthol with 2,4,6-trimethylbenzoic acid promoted by **6a** gave the ester with greater than 99.5% inversion (Table 3, entry 7). When we returned to the use of 4-nitrobenzoic acid, but performed the reaction in DMF, the ester was obtained in good yield but with 99.2% retention (Table 3, entry 8) in sharp contrast with entry 7. The general results observed with L-menthol were shown to also hold for the other chiral alcohols investigated. Thus, (1*R*)-1-phenyl-1-propanol **9** reacted slowly in DMF with 4-nitrobenzoic acid in the presence of **6a** to give the ester with 64% retention and 36% inversion of configuration at the alcohol center (Table 3, entry 9) while bulky phosphorane **6b** provided 95% retention (Table 3, entry 10). The same reaction conducted in toluene and employing 2,4,6-trimethylbenzoic acid proceeded faster and delivered the ester with 95% inversion of configuration (Table 3, entry 11).

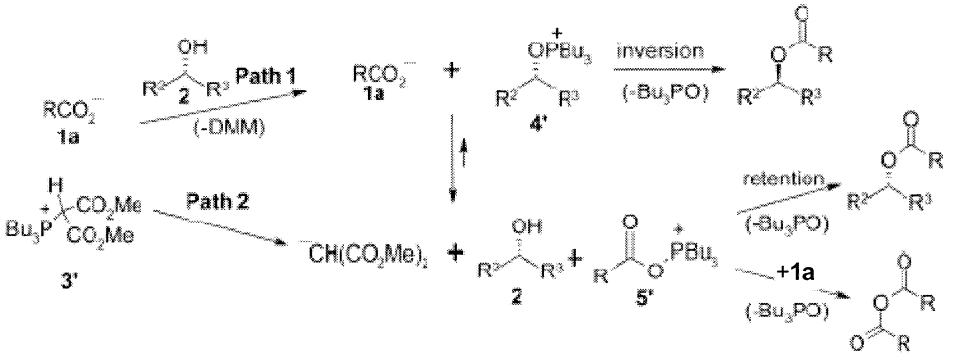
Similarly, (2*S*)-2-hexanol **8** could be esterified yielding the products of inversion or retention in a controlled fashion (Table 3, entries 12-15). The reaction in DMF using the tributylphosphorane **6a** and 4-nitrobenzoic acid for the esterification of non-hindered

alcohols **8** and **9** gave ester with 80% retention maximum, while bulky triisobutylphosphorane **6b** gave up to 97% retention (Table 3, entries 10 and 13) although the reaction conversion was lower than when **6a** was employed.

Overall, the product of inversion is favoured with use of phosphorane **6a** when the reaction is performed in toluene, using a carboxylic acid with one or more ortho-substituents and preferably these being electron releasing groups (i.e. 2,4,6-trimethyl- or 2,6-dimethoxybenzoic acid). The product of retention is favoured when the reaction is performed in DMF with 4-nitrobenzoic acid and is increased as the steric bulk of the trialkyl substituents on the phosphorane increases. In most cases, DMTP **6a** was the reagent of choice in effecting rapid esterification. Interestingly, the triphenylphosphine-derived analogue of **6** was not very effective in promoting the esterification reaction.

The mechanistic underpinnings of the reaction were then investigated. In control experiments we determined that alcohols do not enter into reaction with DMPT **6a** in the absence of any carboxylic acid or proton source. However, carboxylic acids react slowly with **6a** in the absence of alcohol to produce the acid anhydride. The reaction of 2,4,6-trimethylbenzoic acid with **6a** (1:1 molar ratio) conducted at 70^0C in $CDCl_3$ was followed by ^{1}H NMR. After 4 h the anhydride was formed in over 90% yield. Isolation of the anhydride in the absence of an alcohol[43] and formation of the ester with retention of configuration[32b,38] are strongly indicative of the intermediacy of an acyloxyphosphonium ion. We also determined that chiral alcohols do not react with the anhydride that is formed under the conditions of the esterification reaction, indicating that products of retention do not arise by simple alcohol acylation; clearly two competing pathways leading to the products of inversion or retention are operative.

To explain the results obtained in our studies, the mechanism outlined in Scheme 6 is postulated.



Scheme 6. Postulated Mechanisms for the Esterification with DMTP.

Initial protonation of **6a** provides the activated intermediate **3'**, analogous to **3**, Scheme 2. However, since esters with retention of stereochemistry are formed as well as anhydride in certain cases, the major reaction appears to follow Path 2, proceeding via the acyloxyphosphonium ion intermediate **5'**. In contrast to hydrazide ion formation in the Mitsunobu reaction[32b] the only basic anions that can be formed in the above process are the dimethylmalonyl anion (DMM pK_a approximately 10) or the carboxylate anion, formed by proton transfer to DMM. Under these circumstances, base-mediated crossover to Path 1 (**5'** to **4'**) becomes less favorable and a higher degree of retention is expected.

The substituent effect on the reaction *conversion* with 4-substituted benzoic acids (Table 3, entries 1-3) indicates that 4-nitrobenzoic acid forms the acyloxyphosphonium salt (corresponding to **5'**, Scheme 6) with **6a** faster likely due to its greater acidity. High degrees of retention were also observed with the electron-deficient acids. For more electron-rich carboxylic acids (Table 3, entries 2 and 3) the corresponding carboxylate

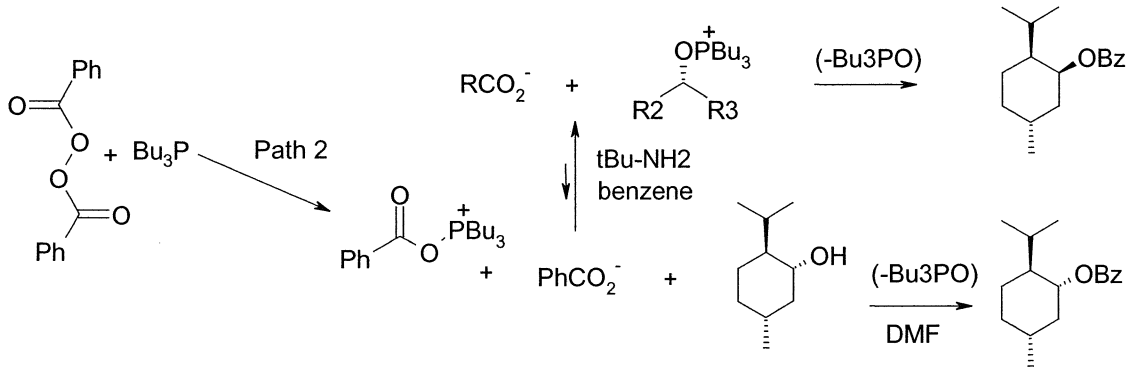
ions are expected to be stronger bases compared to the 4-nitrobenzoate anion. This would lead to increasing conversion of **5'** to **4'** allowing for higher degrees of inversion as the acid becomes more electron rich.

In addition to the importance of the basicity of the reaction media, steric factors on the alcohol, carboxylic acid, and phosphorane, as well as solvent, play important roles on the balance between the competing pathways leading to retention or inversion. In the case involving the 4-nitrobenzoate anion and a hindered alcohol such as menthol, the crossover path is less likely and the reaction proceeds with high retention (99%) in DMF (Table 3, entry 8) and 95% in toluene (Table 3, entry 1). For 4-nitrobenzoic acid and less hindered alcohols **8** and **9** intermediate ratios of retention and inversion are observed (Table 3, entries 9 and 12). As the steric nature of the acid is increased (Table 3, entries 4-7, 11, 14, and 15) the acyloxyphosphonium salt **5'** becomes more hindered and the attack of alcohol on the acyl center becomes slower allowing more alkoxyphosphonium ion **4'** formation leading to higher degrees of inversion and essentially complete inversion when 2,4,6-trimethylbenzoic acid is used (Table 3, entries 7, 11, and 15).

In the cases where the hindered phosphorane **6b** (Table 3, entries 10 and 13) was employed in conjunction with a non-hindered acid, alkoxide or alcohol attack on the acyl carbon (as opposed to phosphorus) of the acyloxyphosphonium salt **5'** is expected to become dominant, resulting in higher degrees of retention.

Further evidence in accord with the postulated mechanism, including base-mediated crossover, was obtained from the following experiments. The independent generation and trapping of acyloxyphosphonium ions can be accomplished oxidatively

through the treatment of a tertiary phosphine with benzoyl peroxide.[43] Thus, a solution of benzoyl peroxide (BPO) in THF was added dropwise to a mixture of L-menthol and tributylphosphine,[43] under our standard esterification conditions (70^0C), and separately with added diisopropylamine.



Scheme 7. Esterification of Menthol Promoted by BPO/Bu_3P Conjunction

The menthyl ester of benzoic acid was formed in good yield in both cases with retention:inversion ratios of 80:20 and 40:60. This first result is very similar to that obtained with phosphorane **6a** and benzoic acid (ratio 81:19). This provides strong evidence for the acyloxyphosphonium[32b] intermediate **5'** and that Path 1 in Scheme 6 may not be operative under our conditions. The result with diisopropylamine is direct independent evidence for the base-mediated competitive crossover path in the esterification reaction promoted by phosphorane **6a** leading to more inversion. The use of triphenylphosphine and BPO was recently shown to generate anhydrides via the acyloxyphosphonium ion even when the reaction was performed in ethanol as solvent.[32b] Only traces of ethyl ester were produced in this process. In contrast to these results, the tri*alkyl*acyloxyphosphonium ion allows esterification to proceed efficiently even when a stoichiometric amount of a hindered alcohol is present.

CONCLUSIONS

I. SUZUKI CROSS-COUPLING REACTION

The phosphonium salt ionic liquid THPC is available in litre quantities and holds a great deal of potential as an economical, recyclable media for metal promoted reactions and process chemistry in general and as we have shown here the Suzuki cross-coupling reaction in particular. Further analysis of the active Pd-catalytic species formed by dissolution of $Pd_2(dba)_3$ in the phosphonium salt ionic liquid and applications of the process to other coupling partners are currently under investigation in our laboratories.

II. ESTERIFICATION REACTION

We have prepared a new class of trialkylphosphorane that promotes the esterification reaction of chiral alcohols allowing controlled inversion or retention of stereochemistry in a predictable manner. The reagents also promote the esterification of achiral substrates with a wide range of carboxylic acid and alcohol partners under neutral conditions. The major advantage of these new reagents is the controlled levels of inversion or retention that can be achieved through choice of reagents and solvent. These results appear to be manifest because no strongly basic species are generated during the reaction allowing clean separation of the two competing pathways available for the reaction. The side products of this reaction, DMM and tributylphosphine oxide, are largely removed by using a basic extraction protocol, simplifying purification. Strong

evidence in favor of the reaction proceeding via an acyloxyphosphonium salt has been uncovered in accord with the mechanism proposed. The question of inversion vs. retention in the esterification reaction of chiral alcohols promoted by phosphorane **6a** is rationalized as competition between direct alcohol acylation by the acyloxyphosphonium ion **5'**, leading to retention, and base-mediated crossover from **5'** to the alkoxyphosphonium ion **4'**, resulting in the product of inversion. The implications of these results for the current view of the standard Mitsunobu esterification are such that the basic hydrazide anion may indeed play a very significant role.[32b,41] Basic anions are also implicated during the esterification reaction carried out with (cyanomethyl)trialkylphosphoranes, such as the elimination of the anion of acetonitrile,[35,36] resulting in inversion of stereochemistry also. By analogy with our results, such basic species may provide a crossover path, via alkoxide anion formation, from an initial acyloxyphosphonium salt to an alkoxyphosphonium salt leading ultimately to esters with inversion of stereochemistry. The results described with the new phosphoranes **6a** and **6b**, along with the recent reports by DeShong[39] and Smith,[40] concerning standard Mitsunobu reagents providing esters (lactones) with retention of stereochemistry draw attention to the fine line between the divergent mechanisms operative in the reaction. While inversion of stereochemistry is the normal outcome for the standard Mitsunobu reaction on chiral secondary alcohols, this should no longer be assumed to be the case, particularly in cases where hindered secondary alcohols are involved. A detailed study concerning the independent generation and trapping of acyloxyphosphonium ions is in progress and will be reported in due course.

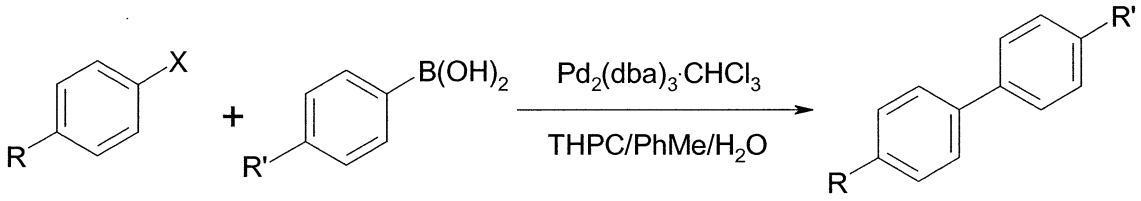
EXPERIMENTAL

I. GENERAL DETAILS

In the reactions described, all starting materials were obtained from Aldrich and used as obtained except those noted below. Tributylphosphine and triisobutylphosphine were obtained from Cytec and 2-chloro-dimethylmalonate from Aldrich, Degussa, and Ubichem. Dry THF was obtained by distillation from sodium-benzophenone, anhydrous DMF used directly (Aldrich *Sure/Seal*^{TM}) and triethylamine distilled over calcium hydride. Methanol, ethanol and isopropanol were redistilled from magnesium turnings before use. Suzuki cross-coupling and esterification reactions were performed individually or in parallel on the Quest 210 Organic Synthesizer. ^{1}H-NMR, ^{13}C-NMR were recorded at 300 and 75 MHz in $CDCl_3$ on a Bruker Avance DPX-300 spectrophotometer. MS analysis was performed on a Kratos Concept 1S spectrometer. FTIR spectra (KBr) were recorded on a Mattson Research Series spectrophotometer. Chiral GC analysis was performed on the HP-6890 with FID and chiral HPLC performed on a Waters 600 series system under the individual conditions described below. Melting points were obtained on an Electrothermal apparatus and reported without correction.

II. SUZUKI CROSS-COUPLING REACTION

General Procedure for Synthesis of Biaryl compounds:



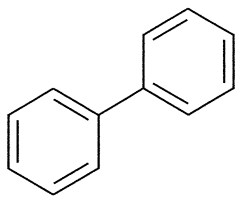
THPC (1.0 mL) was degassed in a dry round bottom flask by pumping under reduced pressure (0.5 mm Hg) for 10 min and then filled with argon. Iodobenzene (0.5 mmol, 1.0 equiv.) and $Pd_2(dba)_3 \cdot CHCl_3$ (0.005 mmol, 0.01 equiv.) were added and the mixture heated briefly using a heat gun to effect an orange solution. After cooling to room temperature K_3PO_4 (1.65 mmol, 3.3 equiv.), phenylboronic acid (0.55 mmol, 1.1 equiv.) distilled water (0.2 mL) and toluene (0.1 mL) were added. When triphenylphosphine (0.01 mmol, 0.02 equiv.) was used (see Table 1) was added as a solution in the added toluene. The solution so obtained was heated under argon at the temperature and for the duration indicated in Table 1. The product biaryls were isolated by using either of two methods.

Method A : Addition of water (5.0 mL) and hexane (15 mL) followed by vigorous shaking and settling for 0.5–1 h. The top hexanes layer was removed and concentrated followed by purification of the biaryl on silica gel. The bottom aqueous phase was removed and discarded leaving the central ionic liquid-catalyst. Use of this method allowed for most efficient catalyst recyclability. The ionic liquid was recharged with phenylboronic acid, iodobenzene and K_3PO_4 and reheated as indicated in Table 1.

Isolated yields ranged from 82–97% for both reactions with no difference being noted in the subsequent reaction. In contrast to the above procedure, exhaustive or continuous extraction (24 h) of the ionic liquid with hexanes results in removal of the catalyst and ionic liquid indicating that both active catalyst and THPC are slightly soluble in hexane.

Method B: In order to determine the isolated yield of the biaryls reported in Table 1 after one run only, the ionic liquid crude reaction mixture was filtered through a silica gel plug, washed with hexanes/ethyl acetate followed by silica gel chromatography of the filtrate. Yields reported in Table 1 are based on isolated mass of the pure biaryls so obtained.

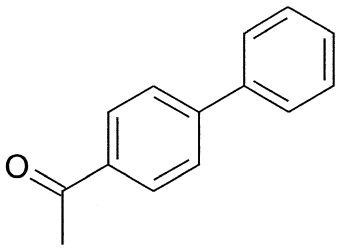
Table 1, Entry 1



1,1'-biphenyl

White solid;
^{1}HNMR ($CDCl_3$): δ 7.42-7.37 (m, 1H), 7.47-7.52 (m, 2H), 7.65 (d, 2H, J=7.1 Hz);
^{13}CNMR ($CDCl_3$): δ 127.6, 127.7, 129.2, 141.6;
MS: m/z (% rel.) 155 (14.8), 154 (100), 153 (30.6), 152 (29.2), 151 (7.8), 77 (10.4), 76 (18.8), 51 (6.7);
HREIMS: calc'd. for $C_{12}H_{10}$ 154.07825; found 154.07762.

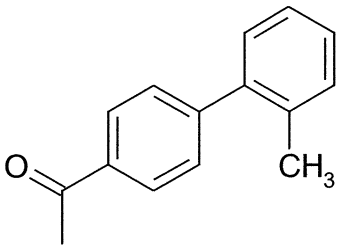
Table 1, Entry 2,10,&14



1-[1,1'-biphenyl]-4-yl-1-ethanone

Off-white solid;
^{1}HNMR ($CDCl_3$): δ 2.67 (s, 3H), 7.43-7.52 (m, 3H), 7.65 (d, 2H, J=7.3 Hz), 7.71 (d, 2H, J=8.3 Hz), 8.06 (d, 2H, J=8.3 Hz);
^{13}CNMR ($CDCl_3$): δ 27.1, 127.6, 127.7, 128.6, 129.3, 129.4, 136.2, 140.3, 146.2, 198.2;
MS: m/z (% rel.) 196 (53.1), 182 (17.0), 181 (100), 153 (21.1), 152 (44.0), 151 (17.1), 76 (24.2), 43 (14.0);
HREIMS: calc'd. for $C_{14}H_{12}O$ 196.08882; found 196.08879.

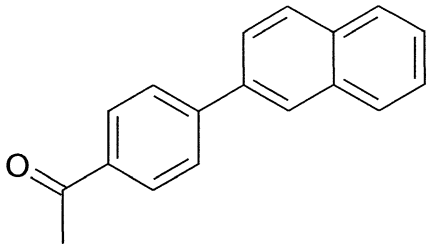
Table 1, Entry 3



1-(2'-methyl-[1,1'-biphenyl]-4-yl)-1-ethanone

Clear colourless oil;
^{1}HNMR ($CDCl_3$): δ 2.31 (s, 3H), 2.68 (s, 3H), 7.25-7.33 (m, 4H), 7.46 (d, 2H, J=8.2 Hz), 8.05 (d, 2H, J=8.2 Hz);
^{13}CNMR ($CDCl_3$): δ 20.8, 27.1, 126.4, 128.3, 128.6, 129.88, 129.91, 131.0, 135.6, 136.0, 141.1, 147.4, 198.3;
MS: m/z (% rel.) 210 (54.7), 196 (15.6), 195 (100), 165 (27.8), 152 (19.1), 97 (18.2), 82 (10.8), 43 (15.9);
HREIMS: calc'd. for $C_{15}H_{14}O$ 210.10447; found 210.10485.

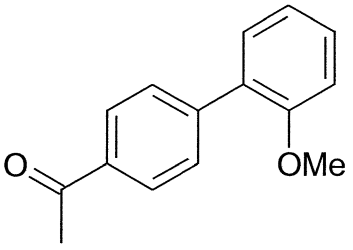
Table 1, Entry 4



1-[4-(2-napthyl)-phenyl]-1-ethanone

Off-white solid;
^{1}HNMR ($CDCl_3$): δ 2.71 (s, 3H), 7.44-7.65 (m, 6H), 7.86-7.96 (m, 3H), 8.12 (d, 2H, J=8.2 Hz);
^{13}CNMR ($CDCl_3$): δ 27.1, 125.7, 125.9, 126.4, 126.8, 127.3, 128.77, 128.82, 130.7, 131.6, 134.2, 136.4, 139.4, 146.2, 198.3;
MS: m/z (% rel.) 247 (22.2), 246 (100), 231 (81.4), 203 (27.5), 202 (81.5), 115 (26.3), 101 (57.1), 100 (22.8);
HREIMS: calc'd. for $C_{18}H_{14}O$ 246.10447; found 246.10417.

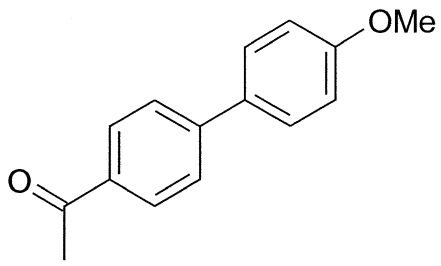
Table 1, Entry 5



1-(2'-methoxy-[1,1'-biphenyl]-4-yl)-1-ethanone

Off-white solid;
^{1}HNMR ($CDCl_3$): δ 2.66 (s, 3H), 3.85 (s, 3H), 7.02-7.10 (m, 2H), 7.35-7.42 (m, 2H), 7.66 (d, 2H, J=8.3 Hz), 8.03 (d, 2H, J=8.3 Hz);
^{13}CNMR ($CDCl_3$): δ 27.1, 56.0, 111.7, 121.4, 128.5, 129.8, 129.9, 130.1, 131.1, 135.9, 144.0, 156.8, 198.3;
MS: m/z (% rel.) 227 (11.8), 226 (65.3), 212 (15.3), 211 (100), 168 (35.7), 139 (16.3), 105 (18.7), 43 (28.3);
HREIMS: calc'd. for $C_{15}H_{14}O_2$ 226.09938; found 226.09943

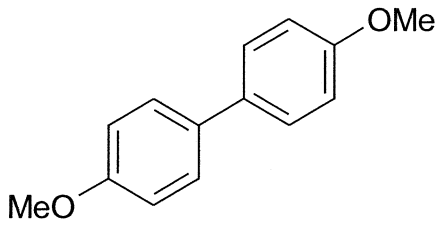
Table 1, Entry 6,11,&15



1-(4'-methoxy-[1,1'-biphenyl]-4-yl)-1-ethanone

Off-white solid;
^{1}HNMR ($CDCl_3$): δ 2.65 (s, 3H), 3.89 (s, 3H), 7.02 (d, 2H, J=8.6 Hz), 7.60 (d, 2H, J=8.8 Hz), 7.67 (d, 2H, J=8.3 Hz), 8.03 (d, 2H, J=8.3 Hz);
^{13}CNMR ($CDCl_3$): δ 27.1, 55.8, 114.8, 127.0, 128.8, 129.3, 132.6, 135.7, 145.8, 160.3, 198.2;
MS: m/z (% rel.) 226 (85.8), 212 (17.0), 211 (100), 168 (22.1), 140 (25.1), 139 (31.8), 105 (23.8), 43 (19.2);
HREIMS: calc'd. for $C_{15}H_{14}O_2$ 226.09938; found 226.09918.

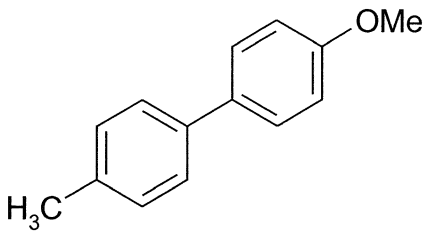
Table 1, Entry 7,13,&16



4,4'-dimethoxy-1,1'-biphenyl

Off-white solid;
^{1}HNMR ($CDCl_3$): δ 3.87 (s, 6H), 6.98 (d, 4H, J=8.7 Hz), 7.50 (d, 4H, J=8.6 Hz);
^{13}CNMR ($CDCl_3$): δ 55.7, 114.5, 128.1, 133.9, 159.1;
MS: m/z (% rel.) 215 (15.5), 214 (100), 200 (9.1), 199 (52.7), 171 (14.3), 139 (7.2), 128 (13.3), 107 (15.0);
HREIMS: calc'd. for $C_{14}H_{14}O_2$ 214.09938; found 214.09917.

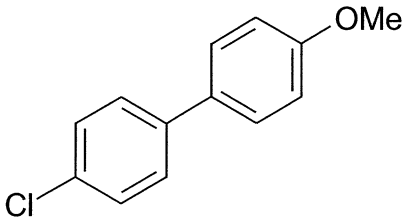
Table 1, Entry 8



4-methoxy-4'-methyl-1,1'-biphenyl

Off-white solid;
^{1}HNMR ($CDCl_3$): δ 2.31 (s, 3H), 3.78 (s, 3H), 6.90 (d, 2H, J=8.6 Hz), 7.16 (d, 2H, J=8.0 Hz), 7.38 (d, 2H, J=8.0 Hz), 7.44 (d, 2H, J=8.7 Hz);
^{13}CNMR ($CDCl_3$): δ 21.5, 55.7, 114.6, 127.0, 128.3, 129.8, 134.1, 136.7, 138.3, 159.3;
MS: m/z (% rel.) 199 (15.5), 198 (100), 183 (30.0), 169 (6.0), 155 (15.1), 153 (6.0), 152 (8.0), 99 (9.2);
HREIMS: calc'd. for $C_{14}H_{14}O$ 198.10447; found 198.10385.

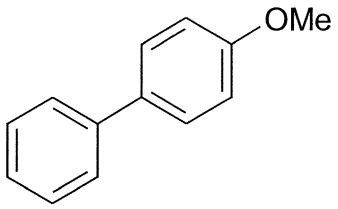
Table 1, Entry 9



4-chloro-4'-methoxy-1,1'-biphenyl

Off-white solid;
^{1}HNMR ($CDCl_3$): δ 3.87 (s, 3H), 7.00 (d, 2H, J=8.7 Hz), 7.40 (d, 2H, J=8.7 Hz), 7.48-7.52 (m, 4H);
^{13}CNMR ($CDCl_3$): δ 55.8, 114.7, 128.3, 128.4, 129.2, 132.9, 133.1, 139.7, 159.7;
MS: m/z (% rel.) 220 (32.1), 219 (14.9), 218 (100), 203 (25.7), 175 (21.0), 139 (17.8), 109 (9.1), 76 (8.7);
HREIMS: calc'd. for $C_{13}H_{11}ClO$ 218.04984; found 218.05028.

Table 1, Entry 12

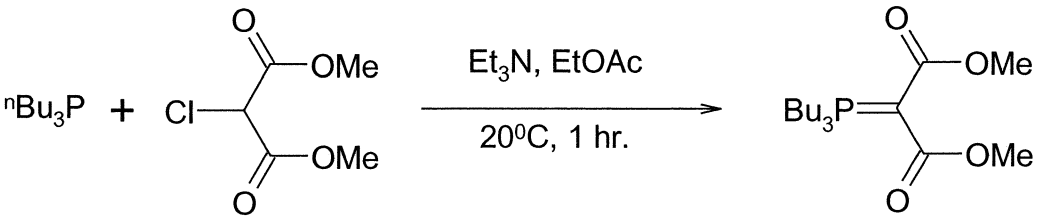


4-methoxy-1,1'-biphenyl

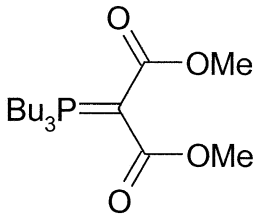
White solid;
^{1}HNMR ($CDCl_3$): δ 3.88 (s, 3H), 7.00-7.03 (m, 2H), 7.28-7.36 (m, 1H), 7.42-7.47 (m, 2H), 7.54-7.60 (m, 4H);
^{13}CNMR ($CDCl_3$): δ 55.7, 114.6, 127.06, 127.14, 127.6. 128.6, 129.1, 134.2, 141.2, 159.5;
MS: m/z (% rel.) 185 (15.6), 184 (100), 169 (25.9), 141 (25.1), 139 (8.6), 115 (21.1), 92 (7.7), 76 (8.9);
HREIMS: calc'd. for $C_{13}H_{12}O$ 184.08882; found 184.08967.

III. ESTERIFICATION REACTION

General Procedure for Synthesis of Phosphorane:



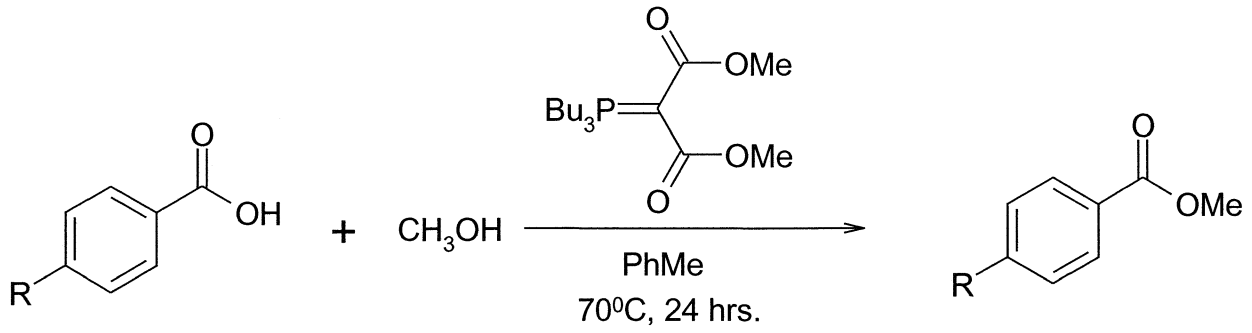
Into a flame-dried round-bottom flask containing dry EtOAc (50.0 ml) was added dimethyl-2-chloromalonate (5.113 ml, 40.0 mmol, 1.0 eq.) and tributylphosphine (10.0 ml, 40.0 mmol, 1.0 eq.) was injected via syringe under argon. The phosphonium salt occasionally crystallizes at this point with no deleterious effects on the reaction. The mixture was cooled in an ice bath while dry Et_3N (5.575 ml, 40.0 mmol, 1.0 eq.) was added dropwise (mild exotherm) to the mixture via syringe. Upon the addition of base the solution becomes a viscous white slurry. The reaction mixture was stirred at room temperature for one hour under argon. The slurry was filtered under positive argon through a short column containing a cotton plug and the precipitated Et_3N-HCl washed thoroughly with EtOAc. The clear filtrate was concentrated by removing the solvent under reduced pressure to give the phosphorane as a colourless oil, 13.105 g, 98.6%. The yield ranged from 98-100% over many attempts.



6a dimethylmalonyltributylphosphorane

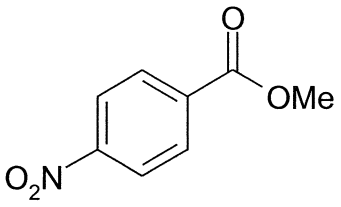
Colourless oil;
^{1}HNMR ($CDCl_3$): 0.75 (t, 3H, J=6.75), 1.21-1.28 (m, 12H), 1.91-1.98 (m, 6H), 3.47 (s, 6H);
^{13}CNMR ($CDCl_3$): 13.2, 21.8 (d, J=55 Hz), 23.6 (d, J=15.4 Hz), 23.9 (d, J=3.8 Hz), 49.9, 168.8 (d, J=14.5 Hz);
^{31}PNMR ($CDCl_3$): 27.8;
MS: m/z (% rel.) 332 (24.3), 303 (53.4), 301 (100), 276 (30.1), 261 (31.1), 219 (22.0), 206 (25.8), 177 (22.8);
HREIMS: calc'd. for $C_{17}H_{33}PO_4$ 332.2116; found 332.2112.
FTIR: 2958, 2936, 2872, 1678, 1640, 1605, 1433, 1312 (P=C), 1076 cm^{-1}.

General Procedure for esterification:



To a flame dried reaction vessel was added the acid (1.8 mmol, 1.5 eq.) under argon. The vessel was then sealed and purged with argon. A 1.0 M solution (PhMe) of the ^{n}tributylphosphorane (1.2 ml, 1.2 mmol, 1.0 eq.) was added via syringe followed by methanol (39ul, 0.96 mmol, 0.8 eq.) under argon. The clear yellowish/orange solution was stirred at 70^{0}C for 24 hours. The solution was cooled to room temperature and an aqueous/organic (0.2N $Na_2CO_{3(aq)}$/EtOAc) workup was performed. The organic layer was washed three times and dried with Na_2SO_4. The solution was gravity filtered through cotton baton and the drying agent was washed thoroughly (4X) with EtOAc. The solvent was removed under reduced pressure to afford a yellowish mixture of crystals and oil as a crude product. The product was purified on a silica gel column (95:5, hexane : ethyl acetate).

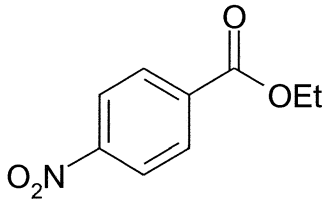
Table 2, Entry 1



Methyl 4-nitrobenzoate

CAS #: 830-03-5
^{1}HNMR ($CDCl_3$): δ 4.00 (s, 3H), 8.23 (d, 2H, J=8.9 Hz), 8.31 (d, 2H, J=8.9 Hz);
^{13}CNMR ($CDCl_3$): δ 52.9, 123.6, 130.8, 135.6, 150.6, 165.3;
MS: m/z (% rel.) 181 (38.7), 150 (100), 120 (11.0), 104 (26.2), 103 (11.6), 76 (21.0), 75 (16.6), 50 (16.5);
HREIMS: calc'd. for $C_8H_7NO_4$ 181.03751; found 181.03803.

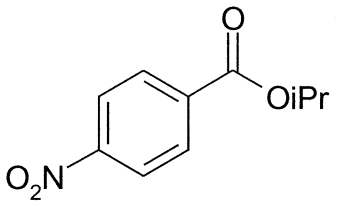
Table 2, Entry 2



Ethyl 4-nitrobenzoate

CAS #: 99-77-4
^{1}HNMR ($CDCl_3$): δ 1.45 (t, 3H, J=7.1 Hz), 4.46 (q, 2H, J=7.2 Hz), 8.23 (d, 2H, J=8.9 Hz), 8.31 (d, 2H, J=8.9 Hz);
^{13}CNMR ($CDCl_3$): δ 14.1, 61.8, 123.7, 130.5, 135.7, 150.3, 165.5.

Table 2, Entry 3

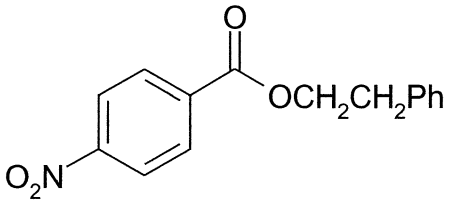


Isopropyl 4-nitrobenzoate

^{1}H-NMR ($CDCl_3$) δ 1.40 (d, 6H, *J*=6.9 Hz), 5.29 (septet, 1H, *J*= 6.4 Hz), 8.20 (d, 2H, *J*=9.0 Hz), 8.27 (d, 2H, *J*=9.0 Hz);
^{13}C-NMR ($CDCl_3$) δ 22.2, 70.1, 123.9, 131.0, 136.6, 150.8, 164.6.

Table 2, Entry 4 **N/A**

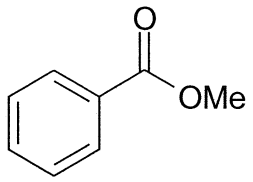
Table 2, Entry 5



2-Phenethyl-4-nitrobenzoate

^{1}H-NMR ($CDCl_3$) δ 3.13 (t, 2H, J= 6.9 Hz), 4.62 (t, 2H, *J*= 6.9 Hz), 7.05-7.44 (m, 5H), 8.18 (d, 2H, *J*=8.3 Hz), 8.29 (d, 2H, *J*=8.3 Hz);
^{13}C-NMR ($CDCl_3$) δ 35.5, 66.7, 123.9, 127.2, 129.05, 129.3, 131.1, 136.0, 137.8, 150.9, 164.97.

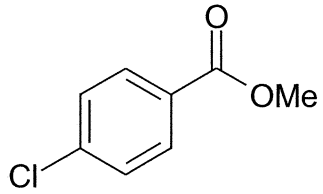
Table 2, Entry 6



Methyl benzoate

CAS #: 93-58-3
^{1}HNMR ($CDCl_3$): δ 3.49 (s, 3H), 7.43-7.48 (m, 2H), 7.55-7.60 (m, 1H), 8.05-8.08 (m, 2H);
^{13}CNMR ($CDCl_3$): δ 52.5, 128.7, 129.9, 130.6, 133.3, 167.5.

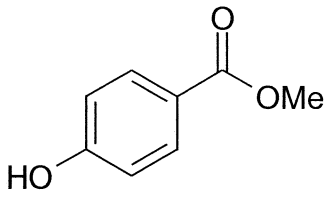
Table 2, Entry 7



Methyl 4-chlorobenzoate

CAS #: 1126-46-1
^{1}HNMR ($CDCl_3$): δ 3.83 (s, 3H), 7.33 (d, 2H, J=8.5 Hz), 7.89 (d, 2H, J=8.3 Hz);
^{13}CNMR ($CDCl_3$): δ 52.6, 129.0, 129.1, 131.3, 139.8, 166.6.

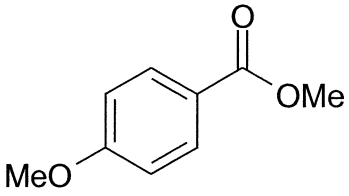
Table 2, Entry 8



Methyl 4-hydroxybenzoate

CAS #: 99-76-3
^{1}HNMR ($CDCl_3$): δ 3.68 (s, 3H), 6.82 (d, 2H, J=8.8 Hz), 7.87 (d, 2H, J=8.8 Hz);
^{13}CNMR ($CDCl_3$): δ 52.4, 115.6, 122.4, 132.3, 161.0, 167.8.

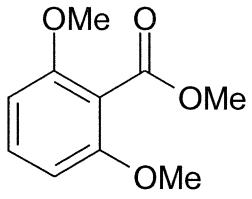
Table 2, Entry 9



Methyl 4-methoxybenzoate

CAS #: 121-98-2
^{1}HNMR ($CDCl_3$): δ 3.77 (s, 3H), 3.80 (s, 3H), 6.83 (d, 2H, J=8.8 Hz), 7.91 (d, 2H, J=8.9 Hz);
^{13}CNMR ($CDCl_3$): δ 52.2, 55.7, 113.9, 123.0, 131.9, 163.7, 167.2.

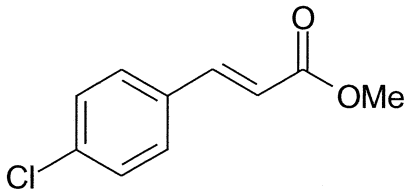
Table 2, Entry 10



Methyl 2,6-dimethoxybenzoate

CAS #: 2065-27-2
^{1}**HNMR** ($CDCl_3$): δ 3.74 (s, 6H), 3.83 (s, 3H), 6.48 (d, 2H, J=8.4 Hz), 7.21 (t, 2H, J=8.3 Hz);
^{13}**CNMR** ($CDCl_3$): δ 52.9, 56.4, 104.3, 113.6, 131.4, 157.7, 167.3.

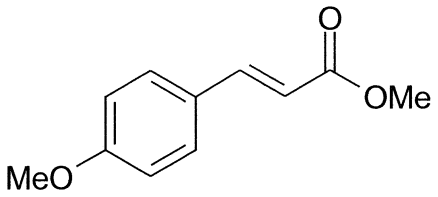
Table 2, Entry 11



Methyl 4-chlorocinnamate

CAS #: 7560-44-3
^{1}**HNMR** ($CDCl_3$): δ 3.51 (s, 3H), 6.13 (d, 1H, J=16.0 Hz), 7.07 (d, 2H, J=8.2 Hz), 7.18 (d, 2H, J=8.4 Hz), 7.34 (d, 1H, J=16.0 Hz);
^{13}**CNMR** ($CDCl_3$): δ 52.2, 118.8, 129.56, 129.61, 133.2, 136.6, 143.8, 167.6.

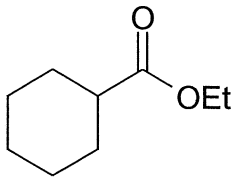
Table 2, Entry 12



Methyl 4-methoxycinnamate

CAS #: 832-01-9
^{1}HNMR ($CDCl_3$): δ 3.61 (s, 3H), 3.65 (s, 3H), 6.14 (d, 1H, J=15.9 Hz), 6.73 (d, 2H, J=8.8 Hz), 7.30 (d, 2H, J=8.7 Hz), 7.47 (d, 1H, J=15.9 Hz);
^{13}CNMR ($CDCl_3$): δ 51.7, 55.4, 114.4, 116.4, 128.1, 130.9, 145.5, 160.3, 167.1.

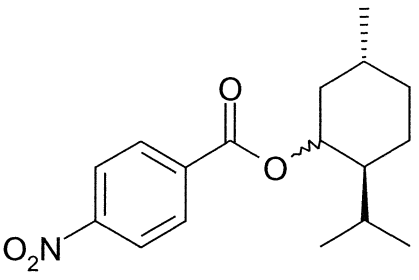
Table 2, Entry 13



Ethyl cyclohexanecarboxylate

CAS #: 3289-28-9
^{1}HNMR ($CDCl_3$): δ 1.26 (t, 3H, J=7.1 Hz), 1.27-1.29 (m, 3H), 1.47-1.69 (m, 3H), 1.75 (m, 2H), 1.90 (m, 3H), 2.30 (m, 1H), 4.12 (q, 2H, J=7.1 Hz);
^{13}CNMR ($CDCl_3$): δ 14.5, 26.0, 26.4, 29.5, 44.4, 59.8, 176.7.

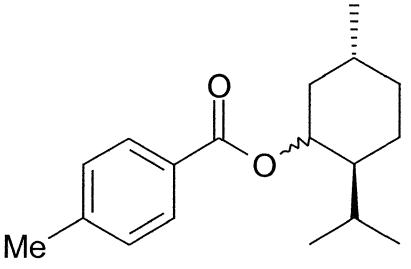
Table 3, Entry 1 & 8



(*1R/S, 2S, 5R*)-1-(4-Nitrobenzoyl)-2-(1'-methylethyl)-5-methylcyclohexan-1-ol

White solid (mp 48-50^{0}C);
^{1}H-NMR ($CDCl_3$): δ 0.80-2.2 (m, 17H), 4.98 (m, 1H), 8.21 (d, 2H, *J*=9.0 Hz), 8.29 (d, 2H, *J*=9.0 Hz);
^{13}C-NMR ($CDCl_3$): δ 16.85, 21.1, 22.4, 23.9, 26.9, 29.8, 31.8, 41.2, 47.5, 76.5, 123.9, 131.0, 136.6, 150.8, 164.6.

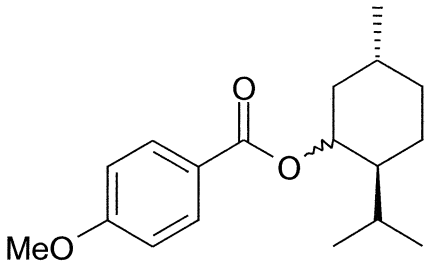
Table 3, Entry 2



(*1R/S, 2S, 5R*)-1-(4-Methylbenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.7-2.2 (m, 17H), 2.43 (s, 3H), 4.94 (m, 1H), 7.26 (d, 2H, *J*= 8.0 Hz), 7.97 (d, 2H, *J*= 8.1 Hz);
^{13}C-NMR ($CDCl_3$): δ 16.9, 21.2, 22.0, 22.4, 24.1, 26.9, 31.8, 34.7, 41.4, 47.7, 74.9, 128.5, 129.9, 131.9, 143.7, 166.5.

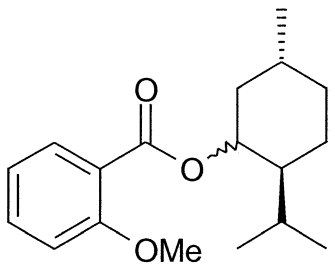
Table 3, Entry 3



(*1R/S, 2S, 5R*)-1-(4-Methoxybenzoyl)-2-(1-methylethyl)-5-methyl-cyclohexan-1-ol

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.65-2.2 (m, 17H), 3.87 (s, 3H), 4.92 (m, 1H), 6.94 (m, 2H), 8.02 (m, 2H);
^{13}C-NMR ($CDCl_3$): δ 16.95, 21.2, 22.4, 24.1, 26.9, 31.8, 34.7, 41.4, 47.7, 55.8, 74.8, 113.9, 123.9, 131.9, 163.6, 166.0.

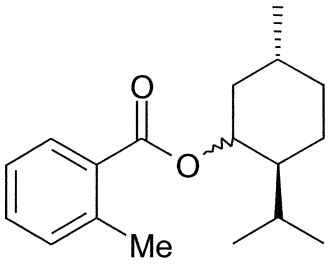
Table 3, Entry 4



(*1R/S 2S, 5R*)-1-(2-Methoxybenzoyl)-2-(1-methylethyl)-5-methyl-cyclohexan-1-ol

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.65-2.2 (m, 17H), 3.87 (s, 3H), 5.43 (broad s, 1H), 6.95-7.10 (m, 2H), 7.45-7.50 (m, 2H), 7.75-7.91 (m, 2H);
^{13}C-NMR ($CDCl_3$): δ 21.2, 21.4, 22.6, 25.7, 26.5, 29.6, 35.4, 39.6, 56.2, 71.9, 112.4, 120.4, 121.1, 132.1, 133.7, 159.8, 165.9.

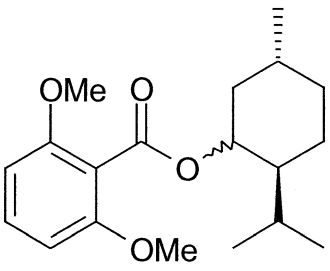
Table 3, Entry 5



(*1R/S, 2S, 5R*)-1-(2-Methylbenzoyl)-2-(1-methylethyl)-5-methyl-cyclohexan-1-ol

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.60-2.2 (m, 17H), 2.56 (s, 3H), 5.40 (broad s, 1H), 6.95-7.35 (m, 3H), 7.85(d, 2H, *J*=8.0 Hz);
^{13}C-NMR ($CDCl_3$): δ 21.2, 21.4, 22.5, 22.6, 25.9, 27.2, 29.7, 35.3, 39.6, 47.4, 71.9, 126.1, 130.7, 131.0, 132.10, 132.13, 140.6, 167.3.

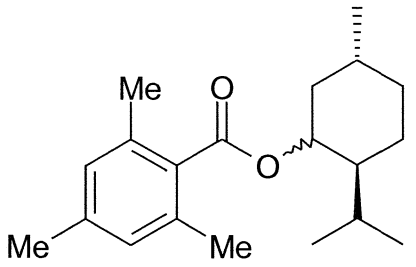
Table 3, Entry 6



(*1R/S, 2S, 5R*)-1-(2, 6-Dimethoxybenzoyl)-2-(1-methylethyl)-5-methyl-cyclohexan-1-ol

White solid;
^{1}H-NMR ($CDCl_3$): δ 0.80-2.3 (m, 17H), 3.80 (s, 6H), 5.44 (broad s, 1H), 6.55 (d, 2H, *J*= 8.4 Hz), 7.27 (t, 2H, *J*= 8.4 Hz);
^{13}C NMR ($CDCl_3$): δ 20.9, 21.5, 22.7, 25.6, 26.7, 29.5, 35.2, 39.5, 47.25, 56.2, 72.7, 104.3, 114.8, 130.8, 157.5, 166.7.

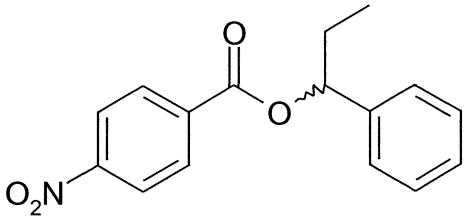
Table 3, Entry 7



(*1R/S*, 2*S*, 5*R*)-1-(2, 4, 6-Trimethylbenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.80-2.34 (m, 17H), 2.31 (s, 3H), 2.33 (s, 6H), 5.54 (broad s, 1H), 6.88 (s, 2H);
^{13}C NMR ($CDCl_3$): δ 19.9, 21.3, 21.46, 21.48, 22.6, 23.1, 25.5, 27.2, 29.3, 35.2, 39.7, 47.45, 72.4, 128.6, 132.6, 134.7, 139.1, 170.5.

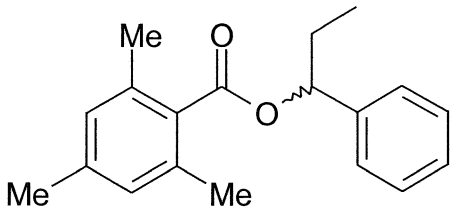
Table 3, Entries 9 & 10



1-Phenyl-1-propyl 4-nitrobenzoate

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.99 (t, 3H, *J*= 7.4 Hz), 1.9-2.25 (m, 2H, *J*= 7.0 Hz), 5.95 (t, 1H, *J*= 6.8 Hz), 7.1-7.52 (m, 5H), 8.29(AB, 4H, *J*= 8.8 Hz);
^{13}C-NMR ($CDCl_3$): δ 10.4, 29.7, 79.6, 123.9, 126.9, 128.6, 129.0, 131.1, 136.3, 140.2, 150.9, 164.4.

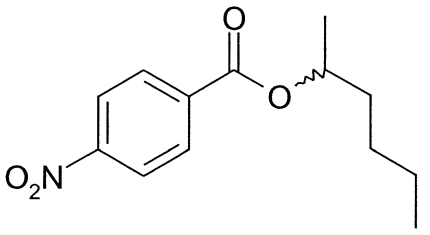
Table 3, Entry 11



1-Phenyl-1-propyl 2, 4, 6-trimethylbenzoate

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 1.05 (t, 3H, *J*= 7.4 Hz), 2.01 (m, 1H), 2.15 (m, 1H), 2.27 (s, 6H), 2.34 (s, 3H), 6.02 (t, 1H, *J*= 6.9 Hz), 6.91 (s, 2H), 7.30-7.58 (m, 5H);
^{13}C-NMR ($CDCl_3$): δ 10.6, 20.0, 21.5, 29.6, 78.8, 127.2, 127.5, 128.4, 128.8, 131.8, 135.3, 139.5, 140.6, 170.5.

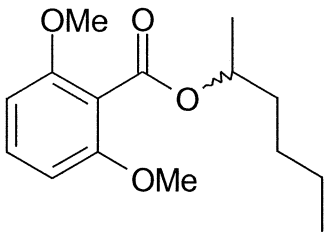
Table 3, Entries 12 & 13



2-Hexyl-4-nitrobenzoate

White solid;
^{1}H-NMR ($CDCl_3$): δ 0.83 (t, 3H, *J*= 6.7 Hz), 1.25-1.32(m, 4H), 1.29 (d, 3H, *J*= 6.2 Hz), 1.33-1.80(m, 2H), 5.11 (m, 1H), 8.17(AB, 4H, *J*= 8.7 Hz);
^{13}C-NMR ($CDCl_3$): δ 14.4, 20.4, 22.9, 27.9, 36.0, 73.5, 123.85, 131.0, 136.7, 150.8, 164.7.

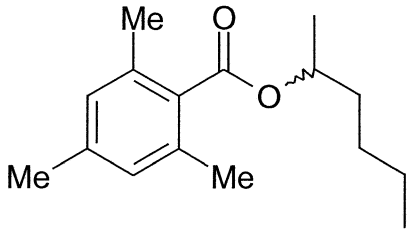
Table 3, Entry 14



2-Hexyl 2,6-dimethoxybenzoate

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.93 (t, 3H, *J*= 6.9 Hz), 1.20-1.50 (m, 4H), 1.34 (d, 3H, *J*= 6.1 Hz), 1.51-1.80 (m, 2H), 3.80 (s, 6H), 5.20 (m, 1H), 6.55 (d, 4H, *J*= 8.4 Hz), 7.28 (t, 1H, *J*= 8.4 Hz);
^{13}C-NMR ($CDCl_3$): δ 14.5, 20.5, 22.9, 27.9, 36.1, 56.3, 72.3, 104.3, 114.3, 131.0, 157.5, 166.6.

Table 3, Entry 15



2-Hexyl 2, 4, 6-trimethylbenzoate

Colourless oil;
^{1}H-NMR ($CDCl_3$): δ 0.95 (t, 3H, *J*= 6.7 Hz), 1.22-1.49 (m, 4H), 1.39 (d, 3H, *J*= 6.4 Hz), 1.50-1.85 (m, 2H), 2.31 (s, 3H), 2.34 (s, 6H), 5.25 (m, 1H), 6.91 (s, 2H);
^{13}C-NMR ($CDCl_3$): δ 14.4, 19.9, 20.4, 21.5, 22.9, 28.0, 36.0, 72.2, 128.7, 132.1, 135.0, 139.3, 170.3.

Esterification of L-menthol with tributylphosphine and benzoyl peroxide:

A solution of benzoyl peroxide (185 mg, 0.64 mmol) in dry THF (0.5 mL) was added dropwise to a stirring mixture of L-menthol (100 mg, 0.64 mmol) and tributylphosphine (160 μL, 0.64 mmol) in 0.5 ml of dry THF at 70°C for 2h. The reaction mixture was then diluted with EtOAc (3.0mL), washed with 0.2N Na_2CO_3(aq.) (2 x 2 ml), dried with Na_2SO_4, filtered and concentrated. The ^{1}H-NMR spectra of the product showed that (*1R/S, 2S, 5R*)-1-(benzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol was formed in approximately 53% conversion leaving 47% unreacted L-menthol. The integration ratios of the C-1 protons for retention : inversion in the ester products was 80 : 20.

Esterification of L-menthol with tributylphosphine and benzoyl peroxide in the presence of diisopropylamine:

A solution of benzoyl peroxide (232.6 mg, 0.96 mmol) in dry THF (1mL) was added dropwise to a stirring mixture of L-menthol (100 mg, 0.64 mmol), tributylphosphine (240 μL, 0.96 mmol) and diisopropylamine (0.45 ml, 3.2 mmol) in 0.5 ml of dry THF at 70°C for 2h. The reaction mixture was then diluted with EtOAc (3.0mL), washed with 2N HCl (2x2mL) then 0.2N Na_2CO_3(aq.) (2 x 2 ml), dried with Na_2SO_4, filtered and concentrated. The ^{1}H-NMR spectra of the product showed that (*1R/S, 2S, 5R*)-1-(benzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol was formed in approximately 47% conversion leaving 53% unreacted L-menthol. The integration ratios of the C-1 protons for retention : inversion in the ester products was 40 : 60.

REFERENCES

[1] Welton, T. *Chem. Rev.* **1999**, 99, 2071.

[2] Zhao, H.; Malhorta, S. V. *Aldrichimica Acta* **2002**, 35, 75.

[3] Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, 39, 3772.

[4] Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, 102, 3667.

[5] Holbery, J.D.; Seddon, K.R. *Clean Prod. Proc.* **1999**, 1, 223.

[6] Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem.* **2001**, 66, 8616.

[7] Rebeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370.

[8] Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, 42, 403.

[9] Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2698.

[10] Bao, W.; Wang, Z.; Li, Y. *J. Org. Chem.* **2003**, 68, 591.

[11] Handy, S. T. *Chem. Eur. J.* **2003**, 9, 2938.

[12] Waffenschmidt, H.; Wasserscheid, P. *J. Mol. Catal. A: Chem.* **2000**, 164, 61.

[13] Bonhote, P.; Dias, A. P.; Papageorgiou, N.; Kalyanasundaram, K.; Gratzel, M. *Inorg. Chem.* **1996**, 35, 1168.

[14] Chauvin, Y.; Gilbert, B.; Guibard, I. *Chem. Commun.* **1990**, 1715.

[15] Chauvin, Y.; Olivier, B. H. *Chemtech* **1995**, 25, 26.

[16] Chauvin, Y.; Einloft, S.; Olivier, B. H. *Ind. Eng. Chem. Res.* **1995**, 34, 1149.

[17] Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, 1, 997.

[18] Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, 1544.

[19] Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249.

[20] Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616.

[21] Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091.

[22] Miyura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457.

[23] Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, 123, 10099.

[24] Littke, A. F.; Dai, C.; Fu, G. C.; *J. Am. Chem. Soc.* **2000**, 122, 4020.

[25] Adjabeng, G.; Brenstrum, T.; Wilson, J.; Frampton, C.; Robertson, A.; Hillhouse, J.; McNulty, J.; Capretta, A. *Org. Lett.* **2003**, 5, 953.

[26] Wolfe J. P.; Singer R. A.; Yang B. H.; Buchwald S. L. *J. Am. Chem. Soc.* **1999**, 121, 9550.

[27] Yin, J.; Rainka, M. P.; Zhang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, 124, 1162.

[28] Liu S. Y.; Choi M. J.; Fu G. C. *Chem. Commun.* **2001**, 2408.

[29] Bedford R. B.; Cazin C. S. J. *Chem. Commun.* **2001**, 1540.

[30] Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

[31] For comprehensive reviews see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

[32] (a) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. (b) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751.

[33] For further mechanistic discussions see: (a) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org Chem.* **1987**, *52*, 4235. (b) Camp, D. D.; Jenkins, I. D. *Aust. J. Chem.* **1988**, *41*, 1835. (c) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257. (d) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, 54, 3045. (e) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, 59, 234. (f) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (g) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843.

[34] Ito, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053.

[35] (a) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081. (b) Uemoto, K.; Kawahito, A.; Matsushita, N.; Sakamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* **2001**, *42*, 905.

[36] (a) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518. (b) Zaragoza, F. *J. Org. Chem.* **2002**, *67*, 4963.

[37] Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049.

[38] Kunz, H.; Schmidt, P. *Chem. Ber.* **1979**, *112*, 3886.

[39] Ahn, C.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1754.

[40] Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.

[41] Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.

[42] Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933.

[43] Greenbaum, M. A.; Denney, D. B.; Hoffman, A. K. *J. Am. Chem. Soc.* **1956**, *78*, 2563.

COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Suzuki cross-coupling reactions of aryl halides in phosphonium salt ionic liquid under mild conditions

James McNulty,*[a] Alfredo Capretta,[a] Jeff Wilson,[a] Jeff Dyck,[a] George Adjabeng[a] and Al Robertson[b]

[a] *Institute of Molecular Catalysis, Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada. E-mail: jmcnulty@chemiris.labs.brocku.ca; Fax: +1 905 682 9020; Tel: +1 905 688 5550 ext. 3405*

[b] *Cytec Canada Inc, PO Box 240, Niagara Falls, Ontario L2E 6T4, Canada. E-mail: Al_Robertson@WE.cytec.com; Fax: +1 905 374 5879; Tel: +1 905 356 9000*

Received (in Cambridge, UK) 15th May 2002, Accepted 18th July 2002
First published as an Advance Article on the web 7th August 2002

The Suzuki cross-coupling of aryl boronic acids with aryl halides, including aryl chlorides, proceeds in the phosphonium salt ionic liquid tetradecyltrihexylphosphonium chloride under mild conditions.

The Suzuki[1] cross-coupling reaction has become a standard method for carbon–carbon bond formation between an sp^2 or non-β-hydride containing electrophile and a boronic acid derivative. Recent application of the reaction to aliphatic electrophiles[2] has expanded its scope considerably. Much recent effort has gone into devising new ligands for this palladium mediated process and various electron rich alkyl phosphines[3] and mixed aryl/alkyl phosphine ligands[4] have been described. Systems allowing for couplings of aryl chlorides are especially sought after due, in part, to the lower cost and ready availability of these substrates and a number of catalysts have recently been developed which promote their Suzuki coupling with boronic acid nucleophiles.[5,6]

Catalyst expense coupled with the non-recyclability of the expended catalyst have been shown to be major drawbacks of these palladium-mediated processes. One solution involves the application of ionic liquids as solvent. Ionic liquids based on alkylimidazolium and other quaternary ammonium/pyridinium salts have emerged as valuable, alternative "green" solvents for catalytic processes over the last few years.[7–10] Using ionic liquids, it is often possible to recycle the active palladium catalyst subsequent to extraction of the organic product and inorganic salts from the ionic liquid, which form a tri-phasic system with water and a non-polar organic solvent. This process has been applied efficiently to the palladium mediated Heck coupling reaction in quaternary nitrogen ionic liquids[11] and can be conducted at room temperature with the application of ultrasound.[12] The Suzuki reaction has also been carried out successfully in imidazolium ionic liquids both thermally[13] and with sonication.[14] Quaternary phosphonium salts are another class of readily available ionic liquid which have received scant attention in the literature. In one case, hexadecyltributylphosphonium bromide was used to effect Heck coupling of aryl halides with acrylic esters,[15] although the reaction was not efficient with aryl chlorides. We report herein on the use of the room temperature ionic liquid tetradecyltrihexylphosphonium chloride (THPC) containing small amounts of water and toluene (single phase) as an efficient reusable media for the palladium catalyzed Suzuki cross-coupling reaction.

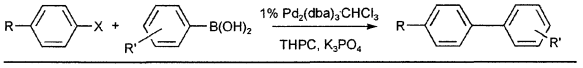
The cross-coupling reactions were found to proceed in THPC using various bases (Et_3N, $^iPr_2NEt$, *etc*) but most efficiently when potassium phosphate and water (added for salt solubility) were employed. In order to maintain complete solubility of both the boronic acid and aryl halide in the ionic liquid, a small amount of toluene was added also. All of the reactions reported in Table 1 were therefore performed in an identical media (THPC, aryl halide, aryl boronic acid, $Pd_2(dba)_3$ (1%), K_3PO_4, H_2O, toluene) with the addition of triphenylphosphine in certain cases as noted.† In many instances, the product biaryl crystallizes from the reaction media as the cross-coupling proceeds.

As can be seen from Table 1 (entries 1–9), the cross-coupling reaction of variously substituted iodobenzenes including electron rich derivatives (Table 1, entry 7) with a variety of arylboronic acids proceeded efficiently in THPC and were all complete within 1 h at 50 °C. The reaction was chemoselective in the case of the mixed halide 4-chloroiodobenzene (Table 1, entry 9). The corresponding aryl bromides (Table 1, entries 11–13) also reacted under these conditions but proved to be somewhat more sluggish. We found that the addition of a catalytic amount of triphenylphosphine allowed for complete conversion and high isolated yields even for the electron rich substrates such as 4-methoxybromobenzene (Table 1, entries 12 and 13). As expected, reactions involving aryl chlorides were considerably slower, however addition of triphenylphosphine and heating at 70 °C allowed high conversion of 4-chloroacetophenone (Table 1, entries 14 and 15). The electron rich 4-methoxychlorobenzene was still slow to react under these conditions (Table 1, entry 16).

Addition of water and hexane to the reaction products in the phosphonium salt ionic liquid results in the formation of a triphasic system that differs from that reported for the imidazolium salts.[11] In the case of imidazolium salts, the ionic liquid is more dense than water and forms the bottom phase with an aqueous central phase and organic layer on top. In the case of THPC, the palladium catalyst remains fully dissolved in the central phosphonium salt layer while the product biaryls are extracted into the top hexane phase and inorganic salts (phosphates/borates) into the lower aqueous phase.

The reaction of phenylboronic acid with iodobenzene has been investigated extensively under our conditions in THPC. The yield obtained from hexane extraction and silica-gel

Table 1 Pd mediated Suzuki cross-coupling of aryl halides and boronic acids in THPC



Entry	X	R	R′	Ligand	Temp./ °C	Time/h	Isolated yield (%)
1	I	H	H	None	50	1	95
2	I	Ac	H	None	50	1	100
3	I	Ac	2-Me	None	50	1	97
4	I	Ac	2-Napthyl	None	50	1	97
5	I	Ac	2-OMe	None	50	1	100
6	I	Ac	4-OMe	None	50	1	99
7	I	OMe	4-OMe	None	50	1	86
8	I	Me	4-OMe	None	50	1	92
9	I	Cl	4-OMe	None	50	1	90
10	Br	Ac	H	PPh_3	50	1	99
11	Br	Ac	4-OMe	PPh_3	50	1	98
12	Br	OMe	H	PPh_3	50	3	99
13	Br	OMe	4-OMe	PPh_3	50	3	95
14	Cl	Ac	H	PPh_3	70	30	84
15	Cl	Ac	4-OMe	PPh_3	70	30	76
16	Cl	OMe	4-OMe	PPh_3	70	30	17

DOI: 10.1039/b204699g

chromatography of the hexane solubles ranged from 82–97% over several runs. On the other hand, direct filtration of the ionic liquid through a short silica-gel column gave slightly higher isolated yields, 95–97%. These results indicate that residual biaryls are still slightly soluble in THPC. The former procedure was more applicable towards the development of a catalyst recycling protocol since chromatography or filtration through silica would make re-use of the catalyst difficult. Thus, following Method A,† when further quantities of iodobenzene, phenylboronic acid and K_3PO_4, *but no further catalyst*, was added to the isolated central ionic liquid, heating again at 50 °C resulted in complete turnover of iodobenzene. Repetition of the work-up Method A gave biphenyl in 82–97% yield (repeated five times) for both the initial and recycled reaction sequences. Thus it is clear that a competent palladium catalyst remains fully dissolved in the phosphonium salt allowing its efficient re-use.

The Suzuki cross-coupling reaction recently reported in imidazolium based ionic liquids requires ultrasonic irradiation to proceed at 30 °C.[14] In addition, inactive Pd black is deposited during the reaction resulting in lower conversions (82–92%) with aryl iodides and bromides and particularly so in the case of electron deficient aryl chlorides (42–65%). Even when pre-formed Pd–biscarbene catalyst is used in this system, conversion of electron deficient aryl chlorides is low to moderate (39–66%).[14] The thermal Suzuki coupling reaction in these imidazolium based ionic liquids does not proceed with aryl chlorides, even at 110 °C.[13] In contrast to these results, complete conversion of aryl iodides and bromides and high conversions with electron deficient chlorides can be achieved in the THPC ionic liquid without the use of a preformed catalyst at 50–70 °C. The rapid coupling of aryl iodides and bromides and high conversions obtained with the aryl chlorides indicate that a very active catalyst is produced in the THPC system. In addition, the higher conversions and recyclability of this Pd THPC–catalyst system indicate the relatively high stability of the active Pd catalyst involved in the Suzuki coupling. Lastly, no homo-coupled products have been observed using the THPC catalyst system reported here.

The phosphonium salt ionic liquid THPC is available in litre quantities and holds a great deal of potential as an economical, recyclable media for metal promoted reactions and process chemistry in general and as we have shown here the Suzuki cross-coupling reaction in particular. Further analysis of the active Pd-catalytic species formed by dissolution of $Pd_2(dba)_3$ in the phosphonium salt ionic liquid and applications of the process to other coupling partners are currently under investigation in our laboratories.

We thank Materials and Manufacturing Ontario (Interact Awards to J. McN. and A. C.) and the Natural Sciences and Engineering Research Council of Canada (Collaborative Research and Development Award) for financial support. We thank Dr Tom Welton for valuable discussions on the imidazolium salt protocol and Dr Dean Toste for advice on the preparation of the Pd catalyst precursors.

Notes and references

† Samples of THPC (trade name Cyphos 3653) can be obtained by contacting Cytec at the address given. A representative procedure for the Suzuki cross-coupling is as follows. THPC (1.0 mL) was degassed in a dry round bottom flask by pumping under reduced pressure (0.5 mm Hg) for 10 min and then filled with argon. Iodobenzene (0.5 mmol, 1.0 equiv.) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.005 mmol, 0.01 equiv.) were added and the mixture heated briefly using a heat gun to effect an orange solution. After cooling to room temperature K_3PO_4 (1.65 mmol, 3.3 equiv.), phenylboronic acid (0.55 mmol, 1.1 equiv.) distilled water (0.2 mL) and toluene (0.1 mL) were added. When triphenylphosphine (0.01 mmol, 0.02 equiv.) was used (see Table 1) it was added as a solution in the added toluene. The solution so obtained was heated under argon at the temperature and for the duration indicated in Table 1. The product biaryls can be isolated by using either of two methods. Method A : Addition of water (5.0 mL) and hexane (15 mL) followed by vigorous shaking and settling for 0.5–1 h. The top hexanes layer was removed and concentrated followed by purification of the biaryl on silica gel. The bottom aqueous phase was removed and discarded leaving the central ionic liquid-catalyst. Use of this method allowed for most efficient catalyst recyclability. The ionic liquid was recharged with phenylboronic acid, iodobenzene and K_3PO_4 and reheated as indicated in Table 1. Isolated yields ranged from 82–97% for both reactions with no difference being noted in the subsequent reaction. In contrast to the above procedure, exhaustive or continuous extraction (24 h) of the ionic liquid with hexanes results in removal of the catalyst and ionic liquid indicating that both active catalyst and THPC are slightly soluble in hexane.

Method B: In order to determine the isolated yield of the biaryls reported in Table 1 after one run only, the ionic liquid crude reaction mixture was filtered through a silica gel plug, washed with hexanes/ethylacetate followed by silica gel chromatography of the filtrate. Yields reported in Table 1 are based on isolated mass of the pure biaryls so obtained.

1 N. Miyura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
2 M. R. Netherton, C. Dai, K. Neuschutz and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 10099.
3 A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020.
4 J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550.
5 S. Y. Liu, M. J. Choi and G. C. Fu, *Chem. Commun.*, 2001, 2408.
6 R. B. Bedford and C. S. J. Cazin, *Chem. Commun.*, 2001, 1540.
7 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
8 R. Sheldon, *Chem. Commun.*, 2001, 2399.
9 C. M. Gordon, *Appl. Catal. A*, 2001, 101.
10 D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today*, 2002, 1.
11 A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. McCormac and K. R. Seddon, *Org. Lett.*, 1999, **1**, 997.
12 R. R. Deshmukh, R. Rajagopal and K. V. Srinivasan, *Chem. Commun.*, 2001, 1544.
13 C. J. Mathews, P. J. Smith and T. Welton, *Chem. Commun.*, 2000, 1249.
14 R. Rajagopal, D. V. Jarikote and K. V. Srinivasan, *Chem. Commun.*, 2002, 616.
15 D. E. Kaufmann, M. Nouroozian and H. Henze, *Synlett*, 1996, 1091.

Typeset and printed by Black Bear Press Limited, Cambridge, England

JOC*Note*

Dimethylmalonyltrialkylphosphoranes: New General Reagents for Esterification Reactions Allowing Controlled Inversion or Retention of Configuration on Chiral Alcohols

James McNulty,*,† Alfredo Capretta,† Vladimir Laritchev,† Jeff Dyck,† and Al J. Robertson‡

Institute of Molecular Catalysis, Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1 Canada, Cytec Canada Inc., P.O. Box 240, Niagara Falls, Ontario L2E 6T4, Canada

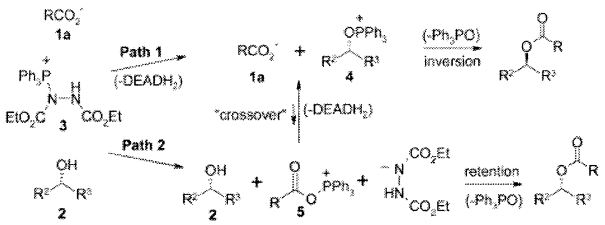
jmcnulty@chemiris.labs.brocku.ca

Received October 31, 2002

Abstract: A new class of trialkylphosphorane has been prepared through reaction of a trialkylphosphine with 2-chlorodimethylmalonate in the presence of triethylamine. These new reagents promote the condensation reaction of carboxylic acids with alcohols to provide esters along with trialkylphosphine oxide and dimethylmalonate. The condensation reaction of chiral secondary alcohols can be controlled to give either high levels of inversion or retention through a subtle interplay involving basicity of the reaction media, solvent, and tuning the electronic and steric nature of the carboxylic acid and steric nature of the phosphorane employed. A coherent mechanism is postulated to explain these observations involving reaction via an initial acyloxyphosphonium ion.

The Mitsunobu reaction[1-4] is widely employed in both condensation and displacement reactions of alcohols with various nucleophiles, normally proceeding with inversion of stereochemistry when chiral alcohols are utilized. The original process employed carboxylic acids **1** (or carboxylates **1a**) as the nucleophile producing ester or lactone products[2a] but has since been extended considerably to include a variety of both heteroatom and carbon-based nucleophiles.[2,5] The most commonly employed promoters for this reaction are dialkyl azodicarboxylates, such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), used in conjunction with triphenylphosphine. New reagents, such as the (cyanomethyl)-

SCHEME 1. Mechanisms for the Mitsunobu Esterification Reaction



trialkylphosphoranes,[6,7] have been developed which also result in inversion of stereochemistry on esterification of chiral alcohols.[6a] These new phosphoranes have also be employed in carbon–carbon[5,7b] and amination[7a] reactions with alcohols.

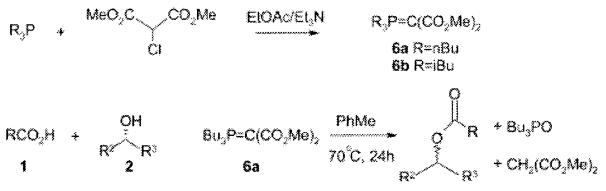
The initial step of the DIAD/triphenylphosphine mediated esterification reaction[3,4] is understood to involve nucleophilic addition of triphenylphosphine to the azodicarboxylate followed by proton transfer from a carboxylic acid to give **3** (Scheme 1). The subsequent steps involve nucleophilic attack of the alcohol **2** on **3** to form an activated alkoxyphosphonium salt **4**[2a] (Scheme 1, Path 1). Finally, S_N2-type displacement by the carboxylate anion on **4** with loss of triphenylphosphine oxide produces the ester with inversion of stereochemistry. Evidence for the existence of an alternative pathway for this reaction proceeding via an acyloxyphosphonium salt (such as **5**, Scheme 1) has been described by Jenkins[8a] and Kunz.[8b] More recently, DeShong[3b,9] demonstrated clear evidence for the involvement of an acyloxyphosphonium salt when hindered alcohols are involved and a further example of a Mitsunobu macrolactonization likely proceeding via the acyloxyphosphonium ion has also recently been described by Smith.[10] In these cases, lactone products were obtained exclusively with retention of stereochemistry. The competitive pathway leading to retention of stereochemistry with hindered alcohols via the acyloxyphosphonium ion **5** is outlined in Scheme 1, Path 2. This scheme also illustrates a competing view of the Mitsunobu reaction involving initial reaction along Path 2. The formation of the basic hydrazide anion leads to subsequent alkoxide formation and "crossover" to the alkoxyphosphonium salt **4**,[3b,11] perhaps proceeding via a mixed alkoxy/acyloxy phosphorane-type intermediate,[4g,8a,12] ultimately yielding the ester with inversion of configuration as the normal outcome. The formation of a basic anion capable of alkoxide formation during the Mitsunobu processes

* Corresponding author.
† Brock University.
‡ Cytec Canada Inc.

(1) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
(2) For comprehensive reviews see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
(3) (a) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. (b) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751.
(4) For further mechanistic discussions see: (a) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org Chem.* **1987**, *52*, 4235. (b) Camp, D. D.; Jenkins, I. D. *Aust. J. Chem.* **1988**, *41*, 1835. (c) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257. (d) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, 54, 3045. (e) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, 59, 234. (f) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (g) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843.
(5) Ito, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053.
(6) (a) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081. (b) Uemoto, K.; Kawahito, A.; Matsushita, N.; Sakamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* **2001**, *42*, 905.
(7) (a) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518. (b) Zaragoza, F. *J. Org. Chem.* **2002**, *67*, 4963.
(8) (a) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049. (b) Kunz, H.; Schmidt, P. *Chem. Ber.* **1979**, *112*, 3886.
(9) Ahn, C.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1754.
(10) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.
(11) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.
(12) Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933.

10.1021/jo026639y CCC: $25.00
Published on Web 01/22/2003

SCHEME 2. Synthesis of Phosphoranes 6 and General Esterification Reaction



described makes it difficult to differentiate between the direct reaction along Path 1 or initial reaction along Path 2 followed by the crossover leading to the necessary alkoxyphosphonium salt **4**.

We have developed a new class of trialkylphosphorane reagent designed to allow for esterification under mild conditions that also helps delineate the competitive pathways described above. These reagents, exemplified by dimethylmalonyltributylphosphorane **6a** (DMTP), are readily prepared by the reaction of a trialkyl phosphine with α-chlorodimethylmalonate in the presence of Et_3N. Scheme 2.

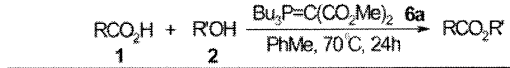
The tributylphosphorane **6a** is a colorless, viscous oil stable under argon at room temperature for at least six months. When exposed to air, the oil slowly solidifies over a period of several days yielding the products of its hydrolysis, tributylphosphine oxide and dimethylmalonate (DMM). The DMTP reagent has been shown to effect the general condensation reaction of a wide variety of carboxylic acids **1** with simple alcohols **2** (Scheme 2) efficiently at neutral pH. The reactions were conducted in dry toluene under argon providing the ester product along with tributylphosphine oxide and DMM. Representative results are summarized in Table 1.

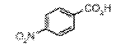
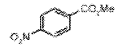
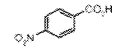
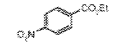
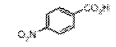
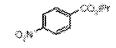
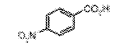
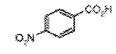
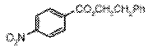
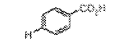
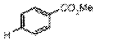
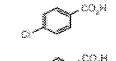
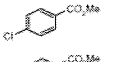
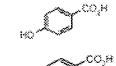
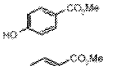
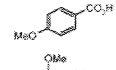
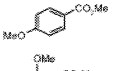
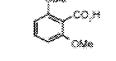
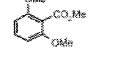
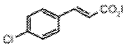
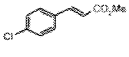
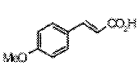
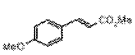
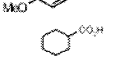
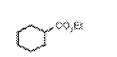
Yields are high with methanol and drop slightly as the bulk of the alcohol increases (Table 1, entries 1−3) while no reaction occurred with the tertiary alcohol *tert*-butanol (Table 1, entry 4). The β-aryl alcohol 2-phenyl-1-propanol reacted cleanly without styrene formation (Table, entry 5), indicating that β-elimination does not occur. Electron-deficient benzoic acids gave slightly better yields (Table 1, entries 1 and 7) with the same alcohol (compare to entries 6 and 8−10). The reaction may also be carried out successfully in the presence of a free phenol (Table 1, entry 8). Finally, cinnamic and aliphatic acids appear to react without difficulty (Table 1, entries 11−13).

A clear advantage gained when using DMTP is that the side products tributylphosphine oxide and DMM can be largely removed by aqueous base partition (0.2 M Na_2CO_3) thereby simplifying purification. The yields reported in Table 1 pertain to the isolated mass of the purified esters obtained by silica gel chromatography.

The stereochemical implications of the reaction were then investigated utilizing chiral alcohols L-menthol **7**, the secondary aliphatic (*2S*)-hexanol **8**, and the benzylic (1*R*)-1-phenyl-1-propanol **9** under a variety of conditions. The reaction could be carried out successfully in toluene, THF, 1,2-dichloroethane, ethyl acetate, or DMF, however, we determined that toluene and DMF gave slightly higher yields and often complementary results in terms of inversion and retention ratios. The overall results are summarized in Table 2. The reaction of L-menthol **7** with 4-nitrobenzoic acid promoted by phosphorane **6a** in

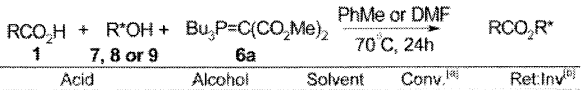
TABLE 1. Esterification Reactions Promoted by Phosphorane 6a

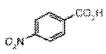
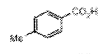
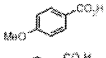
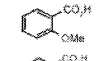
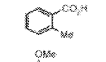
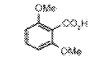
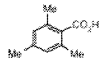
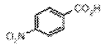
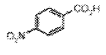
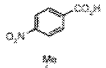
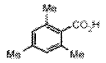
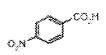
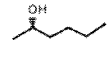
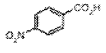
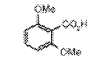
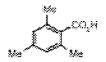


	Acid	Alcohol	Ester	Yield
1		CH_3OH		94%
2		CH_3CH_2OH		86%
3		$(CH_3)_2CHOH$		83%
4		$(CH_3)_3COH$		N.R.
5		$PhCH_2CH_2OH$		88%
6		CH_3OH		70%
7		CH_3OH		98%
8		CH_3OH		75%
9		CH_3OH		75%
10		CH_3OH		77%
11		CH_3OH		70%
12		CH_3OH		81%
13		CH_3CH_2OH		78%

toluene provided the ester with 95% retention of configuration (Table 2, entry 1). The degree of inversion increased as the electron donating ability of the 4-substituent increased (Table 2, entries 1−3) while conversion was higher when electron-deficient 4-substituted benzoic acids were employed. We next investigated the steric nature of the acid with remarkable results. Even a single ortho substituent was seen to have a considerable effect on the outcome of the reaction now delivering the product of inversion with high selectivity (Table 2, entries 4−7). The conversions were lower when mono-ortho-substituted benzoic acids were employed due to competitive formation of the acid anhydride. The reaction of L-menthol with 2,4,6-trimethylbenzoic acid promoted by **6a** gave the ester with greater than 99.5% inversion (Table 2, entry 7). When we returned to the use of 4-nitrobenzoic acid, but performed the reaction in DMF, the ester was obtained in good yield but with 99.2% retention (Table 2, entry 8) in sharp contrast with entry 7. The general results observed with L-menthol were shown to also hold for the other chiral alcohols investigated. Thus, (1*R*)-1-phenyl-1-propanol **9** reacted slowly in DMF with 4-nitrobenzoic acid in the presence of **6a** to give the ester with 64% retention and 36% inversion of configuration at the alcohol center (Table 2, entry 9) while bulky phosphorane **6b** provided 95% retention (Table 2, entry 10). The same reaction conducted in toluene and employing 2,4,6-trimethylbenzoic acid proceeded faster and delivered the ester with 95% inversion of configuration (Table 2, entry 11).

TABLE 2. Esterification Reactions Promoted by Phosphorane 6a



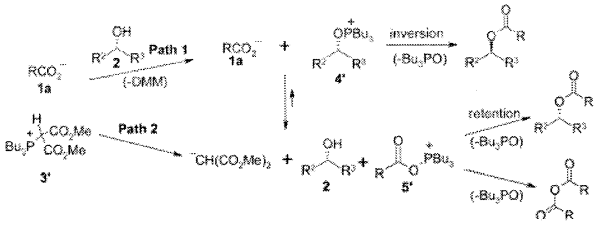
	Acid	Alcohol	Solvent	Conv.[a]	Ret:Inv[b]
1		 7	PhMe	82	95:5
2		7	PhMe	53	63:37
3		7	PhMe	52	33:67
4		7	PhMe	28	2:98
5		7	PhMe	27	5:95
6		7	PhMe	56	4:96
7		7	PhMe	78	<0.5:>99.5
8		7	DMF	76	99.2:0.8
9		 9	DMF	61	64:36
10		9	DMF	27[c]	95:5
11		9	PhMe	83	5:95
12		 8	DMF	71	80:20
13		8	DMF	34[c]	97.0:3.0
14		8	PhMe	85	<0.1:>99.9
15		8	PhMe	84	<0.1:>99.9

[a] Conversions are unoptimized results based on the isolated mass of purified ester after the standard 24 h reaction period. [b] Retention:inversion ratios measured by ^{1}H NMR (menthol) and chiral GC or HPLC in comparison with authentic standards.

Similarly, (2*S*)-2-hexanol **8** could be esterified yielding the products of inversion or retention in a controlled fashion (Table 2, entries 12−15). The reaction in DMF using the tributylphosphorane **6a** and 4-nitrobenzoic acid for the esterification of nonhindered alcohols **8** and **9** gave ester with 80% retention maximum, while bulky triisobutyl phosphorane **6b** gave up to 97% retention (Table 2, entries 10 and 13) although the reaction conversion was lower than when **6a** was employed.

Overall, the product of inversion is favored with use of phosphorane **6a** when the reaction is performed in toluene, using a carboxylic acid with one or more ortho-substituents and preferably these being electron releasing groups (i.e. 2,4,6-trimethyl- or 2,6-dimethoxybenzoic acid). The product of retention is favored when the reaction is performed in DMF with 4-nitrobenzoic acid and is increased as the steric bulk of the trialkyl substituents on the phosphorane increases. In most cases, DMTP **6a** was the reagent of choice in effecting rapid esterification. Interestingly, the triphenylphosphine-derived analogue of **6** was not very effective in promoting the esterification reaction.

SCHEME 3. Postulated Mechanisms for the Esterification with 6a



The mechanistic underpinnings of the reaction were then investigated. In control experiments we determined that alcohols do not enter into reaction with DMPT **6a** in the absence of any carboxylic acid or proton source. However, carboxylic acids react slowly with **6a** in the absence of alcohol to produce the acid anhydride. The reaction of 2,4,6-trimethylbenzoic acid with **6a** (1:1 molar ratio) conducted at 70 °C in $CDCl_3$ was followed by ^{1}H NMR. After 4 h the anhydride was formed in over 90% yield. Isolation of the anhydride in the absence of an alcohol[13] and formation of the ester with retention of configuration[3b,9] are strongly indicative of the intermediacy of an acyloxyphosphonium ion. We also determined that chiral alcohols do not react with the anhydride that is formed under the conditions of the esterification reaction, indicating that products of retention do not arise by simple alcohol acylation; clearly two competing pathways leading to the products of inversion or retention are operative.

To explain the results obtained in our studies, the mechanism outlined in Scheme 3 is postulated. Initial protonation of **6a** provides the activated intermediate **3′**, analogous to **3**, Scheme 1. However, since esters with retention of stereochemistry are formed as well as anhydride in certain cases, the major reaction appears to follow Path 2, proceeding via the acyloxyphosphonium ion intermediate **5′**. In contrast to hydrazide ion formation in the Mitsunobu reaction[3b] the only basic anions that can be formed in the above process are the dimethylmalonyl anion (DMM pK_a approximately 10) or the carboxylate anion, formed by proton transfer to DMM. Under these circumstances, base-mediated crossover to Path 1 (**5′** to **4′**) becomes less favorable and a higher degree of retention is expected.

The substituent effect on the reaction *conversion* with 4-substituted benzoic acids (Table 2, entries 1−3) indicates that 4-nitrobenzoic acid forms the acyloxyphosphonium salt (corresponding to **5′**, Scheme 3) with **6a** faster likely due to its greater acidity. High degrees of retention were also observed with the electron-deficient acids. For more electron-rich carboxylic acids (Table 2, entries 2 and 3) the corresponding carboxylate ions are expected to be stronger bases compared to the 4-nitrobenzoate anion. This would lead to increasing conversion of **5′** to **4′** allowing for higher degrees of inversion as the acid becomes more electron rich.

(13) Greenbaum, M. A.; Denney, D. B.; Hoffman, A. K. *J. Am. Chem. Soc.* **1956**, *78*, 2563.

In addition to the importance of the basicity of the reaction media, steric factors on the alcohol, carboxylic acid, and phosphorane, as well as solvent, play important roles on the balance between the competing pathways leading to retention or inversion. In the case involving the 4-nitrobenzoate anion and a hindered alcohol such as menthol, the crossover path is less likely and the reaction proceeds with high retention (99%) in DMF (Table 2, entry 8) and 95% in toluene (Table 2, entry 1). For 4-nitrobenzoic acid and less hindered alcohols **8** and **9** intermediate ratios of retention and inversion are observed (Table 2, entries 9 and 12). As the steric nature of the acid is increased (Table 2, entries 4−7, 11, 14, and 15) the acyloxyphosphonium salt **5′** becomes more hindered and the attack of alcohol on the acyl center becomes slower allowing more alkoxyphosphonium ion **4′** formation leading to higher degrees of inversion and essentially complete inversion when 2,4,6-trimethylbenzoic acid is used (Table 2, entries 7, 11, and 15).

In the cases where the hindered phosphorane **6b** (Table 2, entries 10 and 13) was employed in conjunction with a nonhindered acid, alkoxide or alcohol attack on the acyl carbon (as opposed to phosphorus) of the acyloxyphosphonium salt **5′** is expected to become dominant, resulting in higher degrees of retention.

Further evidence in accord with the postulated mechanism, including base-mediated crossover, was obtained from the following experiments. The independent generation and trapping of acyloxyphosphonium ions can be accomplished oxidatively through the treatment of a tertiary phosphine with benzoyl peroxide.[13] Thus, a solution of benzoyl peroxide (BPO) in THF was added dropwise to a mixture of L-menthol and tributylphosphine,[13] under our standard esterification conditions (70 °C), and separately with added diisopropylamine. The menthyl ester of benzoic acid was formed in good yield in both cases with retention:inversion ratios of 80:20 and 40:60. This first result is very similar to that obtained with phosphorane **6a** and benzoic acid (ratio 81:19). This provides strong evidence for the acyloxyphosphonium[3b] intermediate **5′** and that Path 1 in Scheme 3 may not be operative under our conditions. The result with diisopropylamine is direct independent evidence for the base-mediated competitive crossover path in the esterification reaction promoted by phosphorane **6a** leading to more inversion. The use of triphenylphosphine and BPO was recently shown to generate anhydrides via the acyloxyphosphonium ion even when the reaction was performed in ethanol as solvent.[3b] Only traces of ethyl ester were produced in this process. In contrast to these results, the tri*alkyl*acyloxyphosphonium ion allows esterification to proceed efficiently even when a stoichiometric amount of a hindered alcohol is present.

In conclusion, we have prepared a new class of trialkylphosphorane that promotes the esterification reaction of chiral alcohols allowing controlled inversion or retention of stereochemistry in a predictable manner. The reagents also promote the esterification of achiral substrates with a wide range of carboxylic acid and alcohol partners under neutral conditions. The major advantage of these new reagents is the controlled levels of inversion or retention that can be achieved through choice of reagents and solvent. These results appear to be manifest because no strongly basic species is generated during the reaction allowing clean separation of the two competing pathways available for the reaction. The side products of this reaction, DMM and tributylphosphine oxide, are largely removed by using a basic extraction protocol, simplifying purification. Strong evidence in favor of the reaction proceeding via an acyloxyphosphonium salt has been uncovered in accord with the mechanism proposed. The question of inversion vs retention in the esterification reaction of chiral alcohols promoted by phosphorane **6a** is rationalized as competition between direct alcohol acylation by the acyloxyphosphonium ion **5′**, leading to retention, and base-mediated crossover from **5′** to the alkoxyphosphonium ion **4′**, resulting in the product of inversion. The implications of these results for the current view of the standard Mitsunobu esterification are such that the basic hydrazide anion may indeed play a very significant role.[3b,11] Basic anions are also implicated during the esterification reaction carried out with (cyanomethyl)trialkylphosphoranes, such as the elimination of the anion of acetonitrile,[6,7] resulting in inversion of stereochemistry also. By analogy with our results, such basic species may provide a crossover path, via alkoxide anion formation, from an initial acyloxyphosphonium salt to an alkoxyphosphonium salt leading ultimately to esters with inversion of stereochemistry. The results described with the new phosphoranes **6a** and **6b**, along with the recent reports by DeShong[9] and Smith,[10] concerning standard Mitsunobu reagents providing esters (lactones) with retention of stereochemistry draw attention to the fine line between the divergent mechanisms operative in the reaction. While inversion of stereochemistry is the normal outcome for the standard Mitsunobu reaction on chiral secondary alcohols, this should no longer be assumed to be the case, particularly in cases where hindered secondary alcohols are involved. A detailed study concerning the independent generation and trapping of acyloxyphosphonium ions is in progress and will be reported in due course.

Acknowledgment. Financial support of this work by NSERC and Materials and Manufacturing Ontario is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026639Y

Acyloxyphosphonium Ion Trapping

The Role of Acyloxyphosphonium Ions and the Stereochemical Influence of Base in the Phosphorane-Mediated Esterification of Alcohols**

James McNulty, Alfredo Capretta, Vladimir Laritchev, Jeff Dyck, and Al J. Robertson*

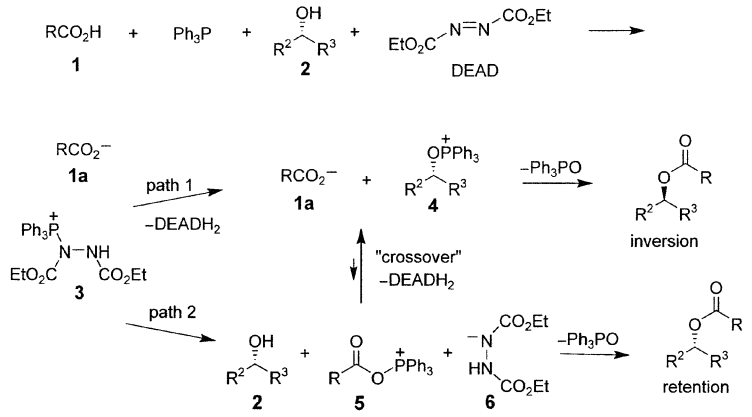
The Mitsunobu reaction[1-4] is widely employed in both condensation and displacement reactions of alcohols with various nucleophiles and normally proceeds with inversion of stereochemistry when chiral secondary alcohols are used. The mechanism of the reaction continues to receive attention and the present view is summarized in Scheme 1. Although the

[*] Dr. J. McNulty, Dr. A. Capretta, Dr. V. Laritchev
Department of Chemistry, McMaster University
1280 Main Street West, Hamilton, Ontario, L8S 4M1 (Canada)
Fax: (+1) 905-522-2509
E-mail: mcnulty@chemistry.mcmaster.ca
J. Dyck
Department of Chemistry, Brock University
St. Catharines, Ontario, L2S 3A1 (Canada)
A. J. Robertson
Cytec Canada Inc.
P.O. Box 240, Niagara Falls, Ontario, L2E 6T4 (Canada)

[**] Financial support was provided by the Natural Sciences and Engineering Research Council of Canada.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200351209



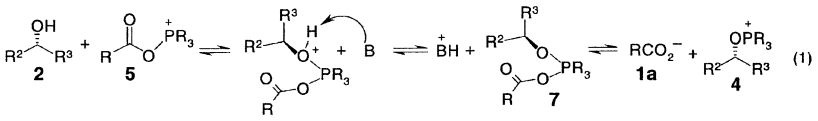
Scheme 1. Mechanism of the Mitsunobu esterification.

initiation and termination steps of the reaction seem clear cut, there is still debate concerning the exact details involved in the intermediate stages of the reaction. The reaction proceeds through the rapid addition[3a] of triphenylphosphane to an azodicarboxylate such as diethyl azodicarboxylate (DEAD), followed by proton transfer from the carboxylic acid to give **1a** and **3** as shown. As the esters obtained are the product of inversion of stereochemistry in the vast majority of cases, it appears that the reaction normally terminates through nucleophilic displacement by **1a** of triphenylphosphane oxide from the activated alkoxyphosphonium ion **4**.

Recent evidence from several laboratories has challenged the original mechanistic hypothesis put forward by Mitsunobu and Yamada,[1,2a] wherein the reaction proceeds directly to the alkoxyphosphonium salt **4** (Scheme 1, path 1). Evidence for the involvement of acyloxyphosphonium ion intermediates **5** has been obtained indirectly over a number of years.[5] Hughes et al.[3b] and Jenkins and co-workers[6] independently reported the isolation of anhydrides from the reaction of acids with DEAD and attributed this to the intermediacy of acyloxyphosphonium ions **5** that Jenkins[6] postulated were in equilibrium with **4**. More recently, DeShong and co-workers,[7] Smith et al.,[8] and De Brabander and co-workers[9] have reported the isolation of products of retention of configuration from the reactions of certain sterically hindered chiral secondary alcohols under standard Mitsunobu conditions.

Retention of stereochemistry is thought to arise through the direct attack of the alcohol at the carbonyl carbon atom of an intermediate acyloxyphosphonium salt. It has been postulated that the normal product obtained from the Mitsunobu reaction may be the result of a competitive crossover reaction mediated by basic species present or generated (such as the hydrazide anion **6**) during the reaction.[7a,10] According to this hypothesis (Scheme 1, path 2), an initial acyloxyphosphonium ion **5** is generated by the attack of the more nucleophilic carboxylate anion **1a**, rather than the alcohol, at the phosphorus center in **3**. The details of the postulated base-mediated crossover to **4** are described in Equation (1). We now report the independent generation of the benzoyloxytributylphosphonium ion, which could be trapped with chiral secondary alcohols under both neutral and basic conditions in the synthesis of esters with either retention or inversion of configuration. Clear evidence was thus obtained for both direct acylation and the postulated base-mediated crossover step.

Acyloxyphosphonium ions have been generated through the addition of a peroxide to a tertiary phosphane, for example, the addition of benzoyl peroxide (BPO) to a solution of triphenylphosphane.[11] When a solution of BPO in *N,N*-dimethylformamide (DMF) was added dropwise to a mixture of L-menthol and tributylphosphane at 70 °C under argon, menthol benzoate was isolated from the reaction mixture in 50 % yield. Spectral analysis of the product showed 97 % retention of stereochemistry, which indicates that direct attack of menthol at the carbonyl carbon of the benzoyloxyphosphonium intermediate had occurred predominantly. These results concur with the postulated intermediacy of acyloxytrialkylphosphonium ions in esterification reactions, generated alternatively by using our recently described phosphorane method.[10] When this method was used, L-menthol reacted with 4-nitrobenzoic acid in DMF to give the corresponding menthol ester with 99.2 % retention of configuration (76 % yield). Recently, Burke and co-workers reported a further independent route to acyloxyphosphonium ions, from trihaloethyl esters. These species also reacted in DMF with L-menthol under nonbasic conditions to provide the corresponding esters with retention of configuration.[12]



(1)

Having demonstrated that the benzoyloxytributylphosphonium ion can be trapped with menthol to yield the desired ester with retention of configuration, we now focused on developing a more synthetically useful process that could provide access to esters with inversion of stereochemistry. We screened a large variety of bases for their ability to effect the postulated crossover step that might lead to inversion. Although essentially any amine added increased the amount of the product of inversion obtained, we quickly determined that bulky primary amines, such as *tert*-butylamine or 1,1,3,3-tetramethylbutylamine, were superior both in terms of the product of inversion/product of retention ratio observed and in terms of the yield of the desired product. The results with L-menthol show that high selectivity in favor of the product of inversion might be anticipated when such hindered bases are present (Table 1, entries 1 and 2), whereas retention of configuration is favored in the absence of a base (Table 1,

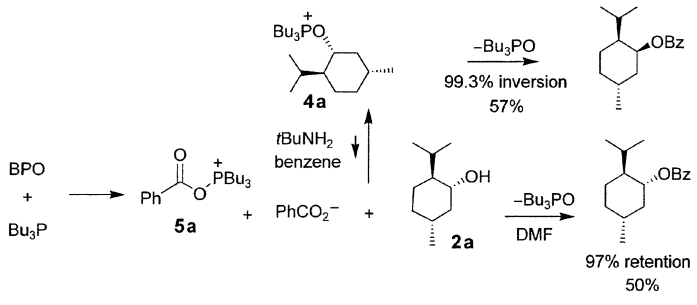
Table 1: Esterification reactions of chiral alcohols promoted by BPO/Bu_3P alone and in the presence of bulky primary amines.

Entry	Alcohol	Base	Method[a]	Ret./inv.[b]	Conv.[c]
1	L-menthol	Me_3CNH_2	A	0.7:99.3	57%
2	L-menthol	$Me_3CCH_2CMe_2NH_2$	A	1.1:98.9	55%
3	L-menthol	–	B	97.0:3.0	50%
4	(2*S*)-hexanol	$Me_3CCH_2CMe_2NH_2$	A	1.9:98.1	73%
5	(2*S*)-hexanol	–	B	55.0:45.0	67%
6	(1*R*)-1-phenyl propanol	$Me_3CCH_2CMe_2NH_2$	A	2.7:97.3	54%
7	(1*R*)-1-phenyl propanol	–	B	43.7:56.3	56%
8	ethyl (*S*)-(−)-lactate	$Me_3CCH_2CMe_2NH_2$	A	5.6:94.4	73%
9	ethyl (*S*)-(−)-lactate	–	B	72.3:27.7	70%

[a] BPO (1.5 equiv) was dissolved in 1.5 mL of benzene (protocol A) or DMF (protocol B) and added dropwise over 70 min to a stirred solution of tributylphosphane (1.5 equiv), the alcohol (1.0 equiv), and the appropriate base (2.5 equiv) in 0.5 mL of benzene or DMF at 70 °C. [b] Product of retention/product of inversion ratio determined by NMR spectroscopy and GC on a chiral phase in comparison with authentic samples. [c] Unoptimized conversion based on mass of purified ester product obtained under standard conditions described.

entry 3). These results are evidence for the base-mediated crossover step proposed in Equation (1). To the best of our knowledge, this is the first report of clear independent evidence for the involvement of a base in such a redox condensation leading to esters with inversion of configuration. These results proved to be general for the chiral secondary alcohols investigated: (2*S*)-2-hexanol (98.1% inversion), (1*R*)-1-phenyl-1-propanol (97.3% inversion), and (2*S*)-ethyl lactate (94.4% inversion).

A relatively clear mechanism can now be proposed to explain the dichotomous results obtained. In contrast with standard Mitsunobu[1] and phosphorane-mediated esterification processes,[11] in the new esterification protocol with inversion of stereochemistry in the presence of BPO/Bu_3P, direct formation of the alkoxyphosphonium ion **4a** is not possible, and the reaction must proceed via **5a** (Scheme 2).



Scheme 2. Generation and trapping of the benzoyloxytributylphosphonium ion **5a** with L-menthol.

When an alcohol is present and in the absence of base, direct acylation of the alcohol predominates, which leads to esters with retention of configuration. This process is also facilitated by the use of DMF as the solvent. In the presence of a base the crossover path becomes dominant, thus leading to the alkoxyphosphonium ion **4a**, and then to esters with inversion of configuration. The function of the base must be either to generate a continuous low concentration of alkoxide to facilitate the crossover step, or to remove a proton with formation of the phosphorane intermediate **7** [Eq. (1)], followed by dissociation to give the required alkoxyphosphonium ion **4**. In either case, the function of the base is to shift the equilibrium shown in Equation (1) to the right and promote the formation of **4**.[12]

In conclusion, we have demonstrated the independent generation of the benzoyloxytributylphosphonium ion and shown that it can be directly trapped with chiral alcohols to yield esters with retention of configuration, or can be converted into an alkoxyphosphonium ion through the addition of a base to yield esters predominantly with inversion of configuration. These studies confirm the existence of a base-induced crossover step and highlight the significance of basic species with regard to the stereochemical outcome of an esterification when such a redox condensation reaction that proceeds via an acyloxytrialkylphosphonium intermediate is used. Attention has often been drawn to the subtle interplay of factors that contribute to the stereochemical outcome in a given case.[6,7a,9,13] The results presented here show that the nature of any basic species present or generated during the reaction can have a profound effect on the stereochemistry of the esterification and thus requires due consideration.

Received: February 18, 2003 [Z51209]

Keywords: acylation · amines · peroxides · phosphanes · synthetic methods

[1] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
[2] For comprehensive reviews, see: a) O. Mitsunobu, *Synthesis* **1981**, 1; b) D. L. Hughes, *Org. React.* **1992**, *42*, 335.
[3] a) D. L. Hughes, R. A. Reamer, J. J. Bergan, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1988**, *110*, 6487; b) D. L. Hughes, R. A. Reamer, *J. Org. Chem.* **1996**, *61*, 2967.
[4] For further mechanistic discussions, see: a) M. Varasi, K. A. M. Walker, M. L. Maddox, *J. Org. Chem.* **1987**, *52*, 4235; b) D. Camp, I. D. Jenkins, *Aust. J. Chem.* **1988**, *41*, 1835; c) D. Crich, H. Dyker, R. J. Harris, *J. Org. Chem.* **1989**, *54*, 257; d) D. Camp, I. D. Jenkins, *J. Org. Chem.* **1989**, *54*, 3045; e) J. A. Dodge, J. I. Trujillo, M. Presnell, *J. Org. Chem.* **1994**, *59*, 234; f) D. L. Hughes, *Org. Prep. Proced. Int.* **1996**, *28*, 127.
[5] For early reports on the involvement of acyloxyphosphonium ions in Mitsunobu-type processes, see: a) H. Kunz, P. Schmidt, *Chem. Ber.* **1979**, *112*, 3886; b) W. Adam, N. Narita, Y. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 1843; c) D. Camp, I. D. Jenkins, *J. Org. Chem.* **1989**, *54*, 3049.
[6] P. J. Harvey, M. von Itzstein, I. D. Jenkins, *Tetrahedron* **1997**, *53*, 3933.

[7] a) C. Ahn, R. Correia, P. DeShong, *J. Org. Chem.* **2002**, *67*, 1751; addendum: C. Ahn, R. Correia, P. DeShong, *J. Org. Chem.* **2003**, *68*, 1176; b) C. Ahn, P. DeShong, *J. Org. Chem.* **2002**, *67*, 1754.
[8] A. B. Smith III, I. G. Safonov, R. M. Corbett, *J. Am. Chem. Soc.* **2002**, *124*, 11102.
[9] X. Liao, Y. Wu, J. K. De Brabander, *Angew. Chem.* **2003**, *115*, 1686; *Angew. Chem. Int. Ed.* **2003**, *42*, 1648.
[10] J. McNulty, A. Capretta, V. Laritchev, J. Dyck, A. J. Robertson, *J. Org. Chem.* **2003**, *68*, 1597.
[11] a) A. M. Pautard, S. A. Evans Jr. , *J. Org. Chem.* **1988**, *53*, 2300; b) M. A. Greenbaum, D. B. Denney, A. K. Hoffman, *J. Am. Chem. Soc.* **1956**, *78*, 2563.
[12] J. J. Hans, R. W. Driver, S. D. Burke, *J. Org. Chem.* **2000**, *65*, 2114.
[13] M. E. Lizarzaburu, S. J. Shuttleworth, *Tetrahedron Lett.* **2002**, *43*, 2157.

